https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club




Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingeladen, uns beizutreten. Bewerben Sie sich!



An 81-year-old man with a smoking history of approximately 60 pack-years was found to have a flank bulge. Twenty years earlier, he underwent surgical resection of three left ribs and a segment of lung for treatment of mesothelioma. He reported onset of the bulge as well as chronic cough a few years after the surgery. The protrusion was soft and compressible, and moved inward during inspiration and outward during expiration. Vesicular breath sounds were heard over the area. What is the most likely diagnosis?

Epidermal cyst

Flail chest

Lung hernia

Ruptured hemidiaphragm

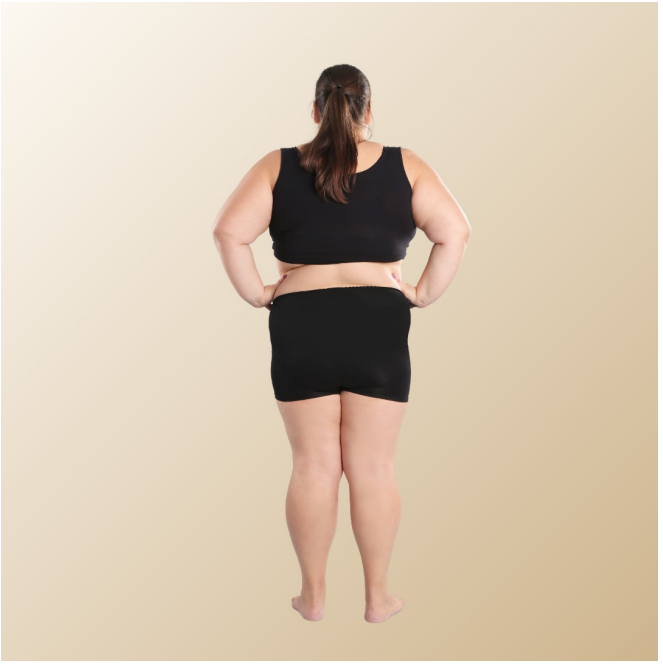
Subcutaneous emphysema

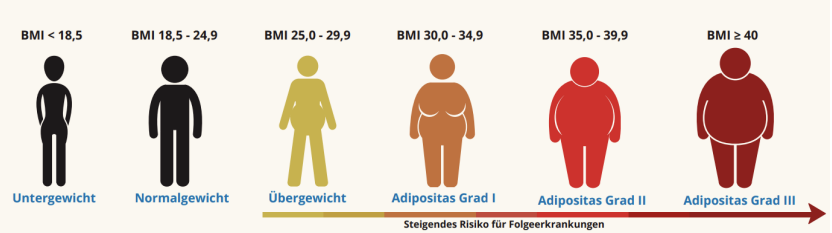
A diagnosis of lung hernia was made. Lung hernias are rare complications of chest-wall trauma or surgery and can be managed conservatively or operatively based upon size and symptom burden.

**Adipositas (Fettleibigkeit)** ist eine chronische Erkrankung, die durch eine übermäßige Vermehrung des Körperfetts gekennzeichnet ist und ab einem Body-Mass-Index (BMI) von 30 kg/m² beginnt. Sie geht weit über ein kosmetisches Problem hinaus und ist eine ernstzunehmende Stoffwechselstörung, die das Risiko für zahlreiche Folgeerkrankungen drastisch erhöht.

Die chronische Fettvermehrung belastet den gesamten Organismus und kann über 60 Folgeerkrankungen nach sich ziehen:

- **Stoffwechsel:** Typ-2-Diabetes, Fettleber und Fettstoffwechselstörungen.
- **Herz-Kreislauf-System:** Bluthochdruck, Arteriosklerose, erhöhtes Risiko für Herzinfarkt und Schlaganfall.
- **Bewegungsapparat:** Vorzeitiger Gelenkverschleiß (Arthrose) durch die mechanische Überlastung.
- **Atmung:** Schlafapnoe (nächtliche Atemaussetzer).
- **Krebsrisiko:** Erhöhte Wahrscheinlichkeit für bestimmte Krebsarten (z.B. Darm-, Brust- oder Gebärmutterkrebs).





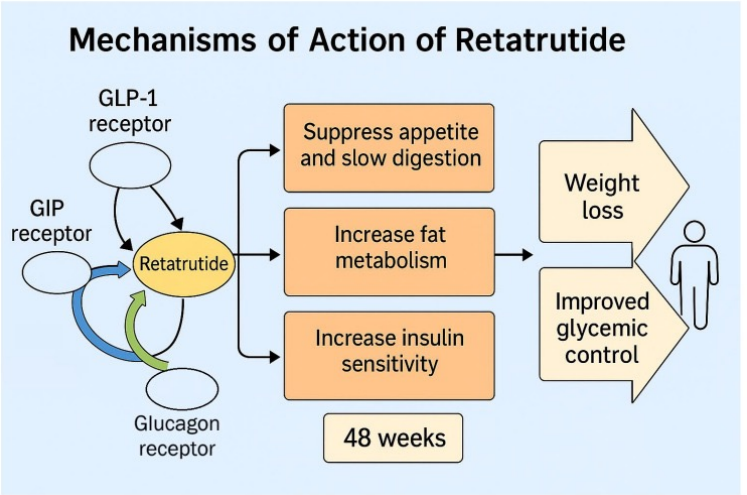

(1 Milliarde)

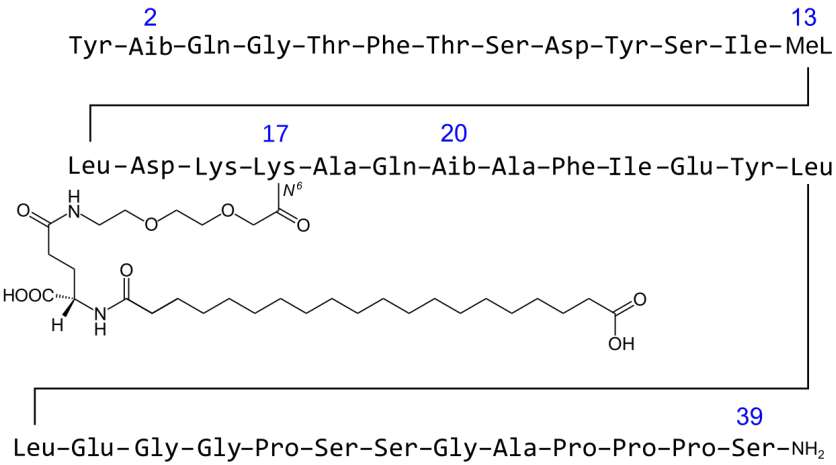
**Retatrutid** ist ein experimenteller Dreifach-Hormonrezeptoragonist (Triple-Agonist), der von dem US-amerikanischen Pharmakonzern **Eli Lilly** entwickelt wird.

**Wirkmechanismus**

Im Gegensatz zu älteren Abnehmspritzen wie Semaglutid (GLP-1-Rezeptoragonist) oder Tirzepatid (GLP-1- und GIP-Rezeptoragonist) greift Retatrutid an **drei** verschiedenen Rezeptoren gleichzeitig an:

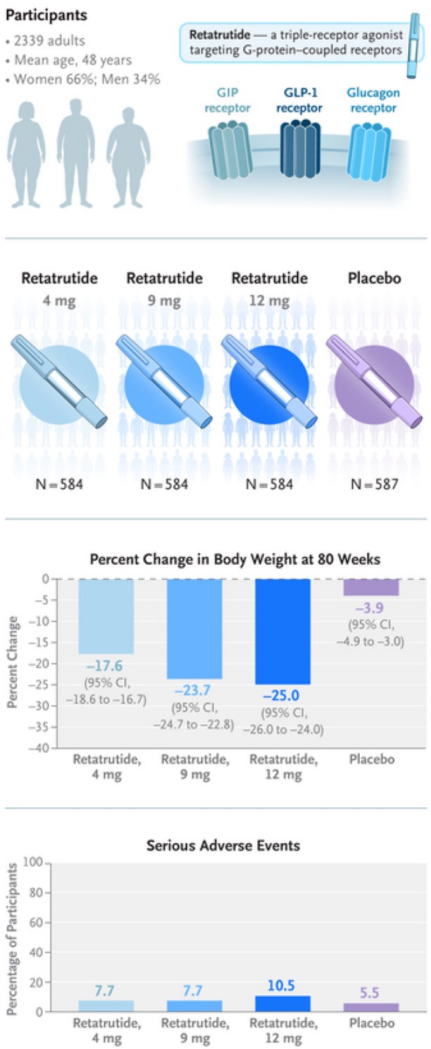
- **GLP-1-Rezeptor:** Verzögert die Magenentleerung und fördert das Sättigungsgefühl.
- **GIP-Rezeptor:** Unterstützt die Insulinsekretion und dämpft das Hungergefühl.
- **Glucagon-Rezeptor:** Kurbelt den Energieumsatz (Grundumsatz) an und unterstützt den Abbau von Leber- und Körperfett.



# Retatrutide, a Triple Hormone Receptor Agonist, for Treatment of Obesity

Retatrutide is a triple-receptor agonist of glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon receptors. In this phase 3, randomized, double-blind trial, we assigned adults with obesity without diabetes to receive a once-weekly subcutaneous injection of retatrutide (at a dose of 4 mg, 9 mg, or 12 mg) or placebo for 80 weeks. Primary outcomes (evaluated in the 9-mg and 12-mg groups each vs. placebo) were the percent change in body weight and the change in the WOMAC pain score (ranging from 1 to 10, with higher scores indicating worse pain) in the subgroup of 574 participants with knee osteoarthritis and the change in the apnea–hypopnea index in the 243 participants with obstructive sleep apnea. For weight-related end points, intercurrent events were handled by a treatment-regimen estimand (intention-to-treat [ITT]). For end points in participants with knee osteoarthritis or obstructive sleep apnea, a hybrid-treatment estimand was applied, with a hypothetical strategy for intercurrent events suggesting treatment failure; ITT results are also reported.



Because obesity is a heterogeneous disease, medications that act through multiple mechanisms may provide the possibility of greater weight reduction and improved health outcomes.

Retatrutide is a triple-receptor agonist targeting the G-protein–coupled receptors for glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon. In a phase 2 trial involving participants with obesity, once-weekly subcutaneous retatrutide (at a dose of 12 mg) resulted in a mean weight reduction of 24.2% at 48 weeks and improved multiple cardiometabolic measures, including waist circumference, systolic and diastolic blood pressure, glycated hemoglobin, and lipid levels. In a substudy, the same regimen of retatrutide resulted in a significant reduction in liver fat. In our current phase 3 trial (TRIUMPH-1), we evaluated the efficacy and safety of retatrutide with respect to obesity as well as knee osteoarthritis and obstructive sleep apnea in participants with obesity without diabetes.

**Participants**

Adults (≥18 years of age) with obesity who did not have diabetes were eligible to participate in the trial. Obesity was defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 30 or a BMI ranging from 27 to less than 30 in participants with at least one complication of obesity. Enrollment was enriched for participants with a BMI of at least 35 (target enrollment, 80%).

**Procedures**

The participants were randomly assigned to receive 80 weeks of once-weekly subcutaneous retatrutide (at a dose of 4 mg, 9 mg, or 12 mg) or placebo, with randomization stratified according to prediabetes status, sex, and eligibility for either basket trial. All the participants received counseling with respect to physical activity and healthy diet without purposeful caloric restriction. A fixed dose escalation protocol was used to reach the assigned dose. Up to two permanent dose reductions were permitted to ameliorate gastrointestinal adverse events during the first 20 weeks and at any time to address inadequate food or fluid intake, a BMI 22.

**End Points and Assessments**

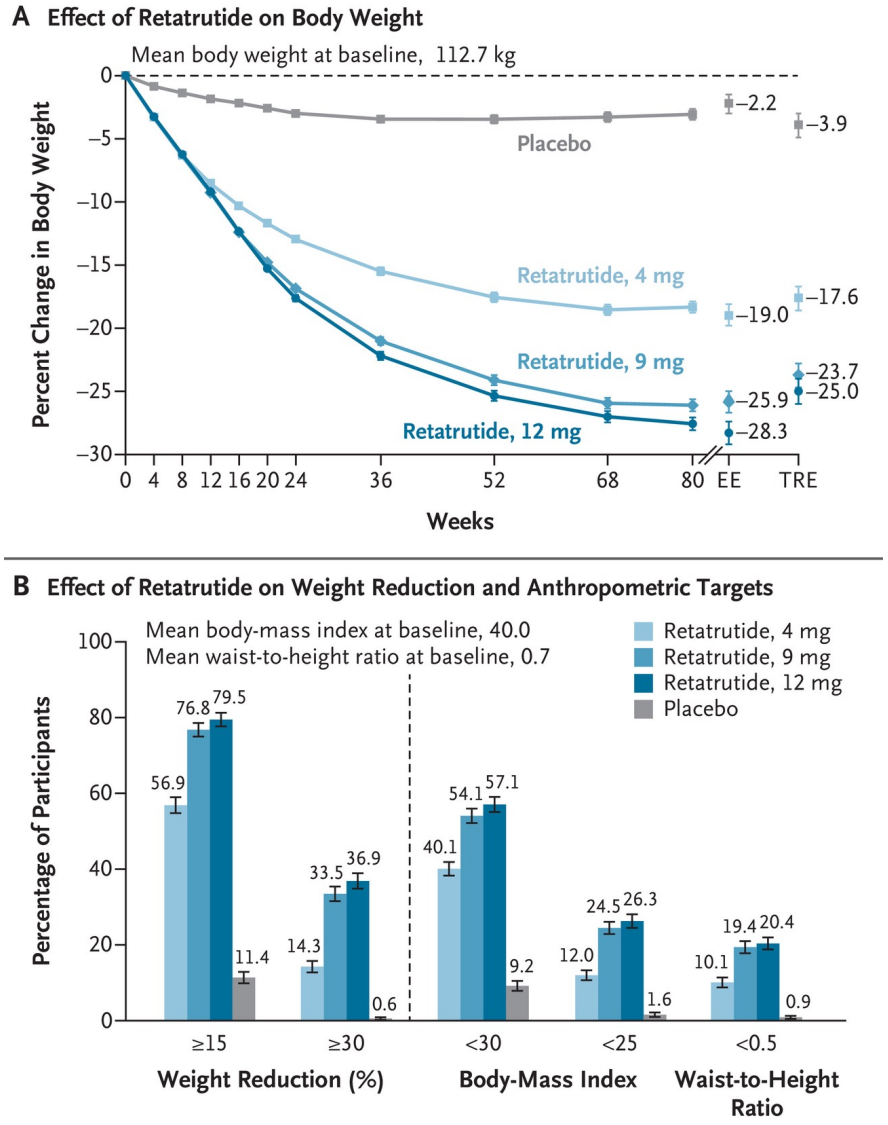
The primary end points were the percent change in body weight (in the main trial), the change in the score on the pain subscale (which ranges from 0 to 10, with higher scores indicating worse pain).

## Baseline

| Characteristic | Retatrutide | | | Placebo N=587 |
|---|---|---|---|---|
| | 4 mg (N=584) | 9 mg (N=584) | 12 mg (N=584) | |
| Age — yr | 48.3±12.0 | 48.8±12.4 | 48.4±12.2 | 48.7±12.1 |
| Female sex — no. (%)† | 382 (65.4) | 383 (65.6) | 383 (65.6) | 385 (65.6) |
| Body weight — kg | 113.3±26.2 | 112.2±24.1 | 113.0±23.9 | 112.3±24.7 |
| Body-mass index‡ | | | | |
| Mean | 40.3±7.3 | 40.0±7.2 | 40.0±6.8 | 39.8±6.9 |
| ≥35 — no. (%) | 462 (79.1) | 451 (77.2) | 449 (76.9) | 448 (76.3) |
| Waist circumference — cm | 118.4±16.2 | 118.0±15.7 | 118.8±15.5 | 118.2±16.0 |
| Systolic blood pressure — mm Hg | 127.3±13.4 | 126.7±13.5 | 126.3±12.7 | 127.0±12.5 |
| Lipid measures — mg/dl | | | | |
| Triglycerides | 133.8±67.2 | 131.0±57.1 | 138.1±103.7 | 134.6±63.3 |
| Non-HDL cholesterol | 142.9±35.1 | 144.2±36.5 | 144.3±36.4 | 145.5±37.3 |
| Prediabetes — no. (%)§ | 199 (34.1) | 225 (38.5) | 207 (35.4) | 214 (36.5) |
| Fasting insulin — mIU/liter | 22.2±17.0 | 21.8±17.6 | 22.7±16.1 | 22.1±16.2 |
| High-sensitivity C-reactive protein — mg/liter | 6.6±8.0 | 6.6±10.4 | 6.5±8.1 | 6.1±6.6 |
| SF-36v2 acute form physical functioning domain score¶ | 46.1±9.3 | 46.6±9.3 | 45.7±10.0 | 46.0±9.4 |
| IWQOL-Lite-CT‖ | | | | |
| Physical function composite score | 52.3±25.9 | 52.2±25.1 | 51.0±26.3 | 49.9±25.3 |
| Psychosocial composite score | 54.6±24.4 | 54.1±24.3 | 52.8±24.3 | 53.2±23.9 |

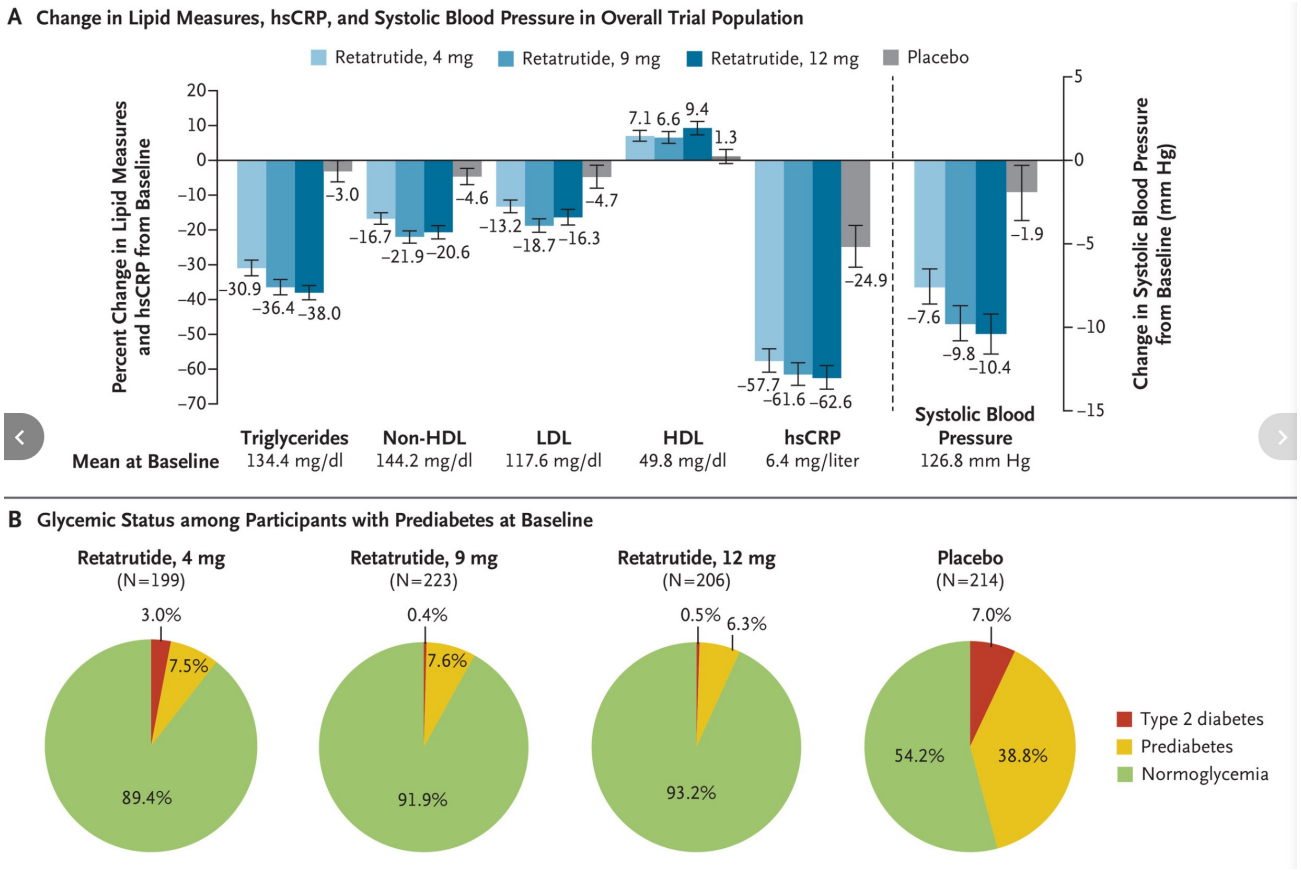
## Adverse events

| Adverse Event | Retatrutide | | | Placebo (N=586) |
|---|---|---|---|---|
| | 4 mg (N=584) | 9 mg (N=583) | 12 mg (N=582) | |
| | *number of participants (percent)* | | | |
| Any adverse event after the start of treatment | 508 (87.0) | 519 (89.0) | 519 (89.2) | 473 (80.7) |
| Serious adverse event | 45 (7.7) | 45 (7.7) | 61 (10.5) | 32 (5.5) |
| Death† | 0 | 3 (0.5) | 1 (0.2) | 2 (0.3) |
| Leading to discontinuation from trial‡ | 6 (1.0) | 8 (1.4) | 16 (2.7) | 10 (1.7) |
| Leading to discontinuation of retatrutide or placebo‡ | 24 (4.1) | 38 (6.5) | 65 (11.2) | 27 (4.6) |
| Gastrointestinal disorder leading to discontinuation of retatrutide or placebo | 13 (2.2) | 22 (3.8) | 27 (4.6) | 7 (1.2) |
| Adverse event in ≥10% of participants§ | | | | |
| Nausea | 167 (28.6) | 224 (38.4) | 247 (42.4) | 87 (14.8) |
| Diarrhea | 147 (25.2) | 199 (34.1) | 186 (32.0) | 79 (13.5) |
| Constipation | 139 (23.8) | 151 (25.9) | 152 (26.1) | 64 (10.9) |
| Vomiting | 62 (10.6) | 133 (22.8) | 147 (25.3) | 28 (4.8) |
| Decreased appetite | 75 (12.8) | 78 (13.4) | 96 (16.5) | 34 (5.8) |
| Upper respiratory tract infection | 83 (14.2) | 71 (12.2) | 76 (13.1) | 68 (11.6) |
| Dizziness | 29 (5.0) | 52 (8.9) | 70 (12.0) | 18 (3.1) |
| Dyspepsia | 46 (7.9) | 52 (8.9) | 63 (10.8) | 22 (3.8) |
| Abdominal pain | 41 (7.0) | 34 (5.8) | 60 (10.3) | 11 (1.9) |
| Fatigue | 43 (7.4) | 62 (10.6) | 59 (10.1) | 21 (3.6) |
| Adverse event of special interest and other safety topics | | | | |
| Dysesthesia: skin burning sensation and related adverse events | 30 (5.1) | 72 (12.3) | 73 (12.5) | 5 (0.9) |



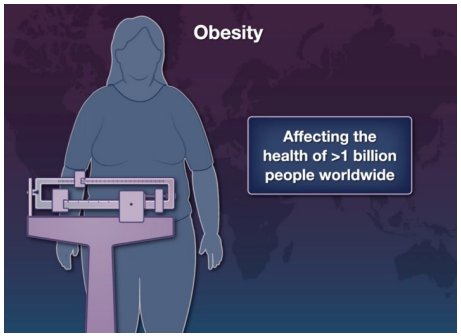

**Effect of Retatrutide on Body Weight.**

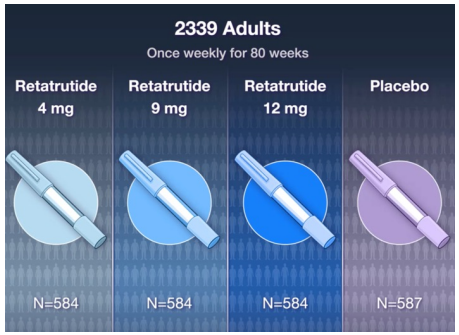
Panel A shows the percent change in body weight from baseline to week 80 (controlled for type I error). The curves on the left show changes from week 0 to week 80 on the basis of observed means during treatment according to the efficacy estimand data-point set; the I bars indicate standard errors. The data at the right of the curves show a model-based estimate with 95% confidence intervals derived from a mixed model for repeated measures for the efficacy estimand (EE) and a model-based estimate with 95% confidence intervals derived from an analysis of covariance for the treatment-regimen estimand (TRE; P<0.001 for all comparisons with placebo). Panel B shows the percentage of participants with reductions in body weight of 15% or more and 30% or more (controlled for type I error), along with the percentage of participants who reached the body-mass index targets of less than 30 or less than 25 and the waist-to-height ratio target of less than 0.5 (not controlled for type I error) at week 80 for the treatment-regimen estimand. Data are model-based estimates, and standard errors are derived from a logistic-regression model with imputed data. P<0.001 for all comparisons with placebo for weight-reduction thresholds. Data regarding the percentage of participants with body-weight reductions of at least 5%, 10%, 20%, 25%, and 35% are provided in Figure S7, and data for the efficacy estimand are provided in Figure S8.

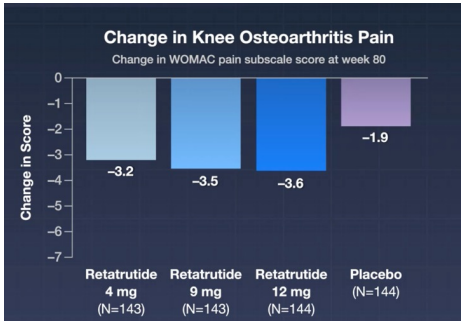


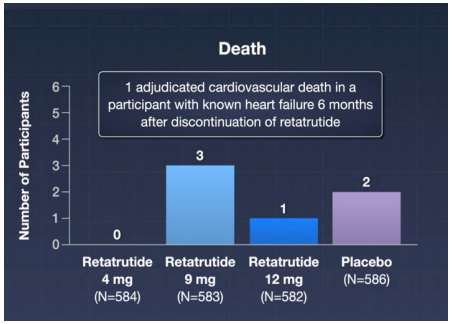

**Effect of Retatrutide on Health Outcomes.**

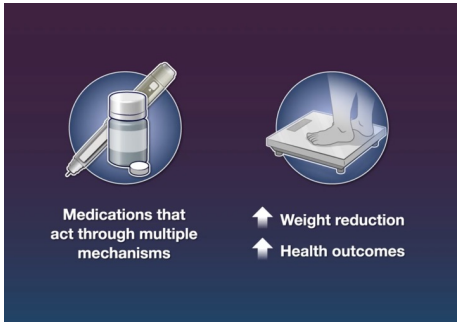
Data are model-based estimates with 95% confidence intervals at week 80, as calculated with the treatment-regimen estimand unless otherwise specified. Panel A shows the percent change in lipid measures, the percent change in the high-sensitivity C-reactive protein (hsCRP), and the change in systolic blood pressure (SBP) in the overall trial population (controlled for type I error except for low-density lipoprotein [LDL] and high-density lipoprotein [HDL]). P<0.001 for all comparisons with placebo. Data for the efficacy estimand are provided in Figures S16 to S18. Panel B shows the percentage of participants with normoglycemia, prediabetes, and type 2 diabetes at week 80 among the participants who had prediabetes at baseline for the treatment-regimen data- points set. Type 2 diabetes was adjudicated by a clinical end-point committee; participants with an adjudicated diagnosis of type 2 diabetes at any time during the trial were classified as having type 2 diabetes at week 80. Remaining glycemic status at week 80 was assessed at the last postbaseline laboratory visit at which each participant had at least one of the following: measurement of fasting glucose, oral glucose tolerance, or glycated hemoglobin. Classification as prediabetes required at least two values within the following ranges: fasting glucose level, 100 to 125 mg per deciliter; 2-hour glucose level, 140 to 199 mg per deciliter; or glycated hemoglobin level, 5.7 to 6.4%, all according to the 2023 American Diabetes Association Standards of Medical Care in Diabetes. Data for the efficacy estimand are provided in Figure S20.

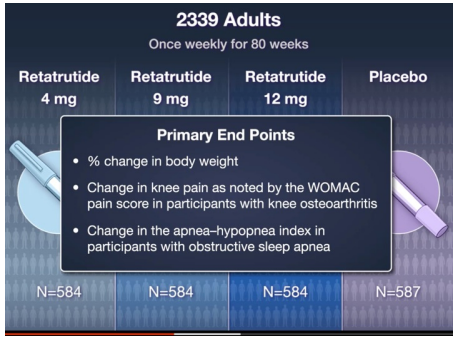

Obesity
Affecting the health of >1 billion people worldwide

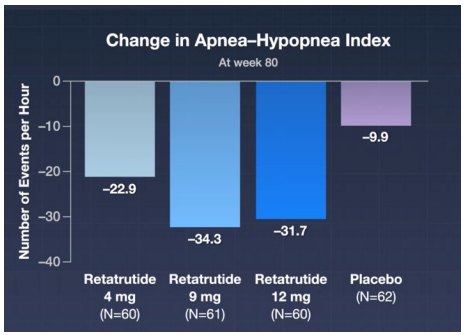

2339 Adults
Once weekly for 80 weeks
Retatrutide 4 mg
Retatrutide 9 mg
Retatrutide 12 mg
Placebo
N=584
N=584
N=584
N=587

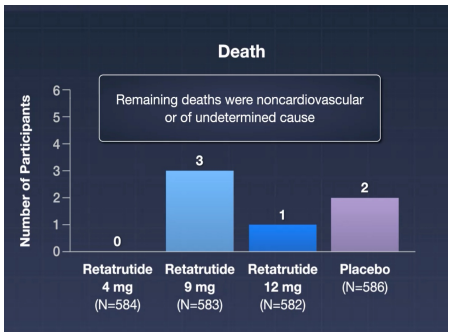

Change in Knee Osteoarthritis Pain
Change in WOMAC pain subscale score at week 80
Change in Score
0
−1
−2
−3
−4
−5
−6
−7
−3.2
−3.5
−3.6
−1.9
Retatrutide 4 mg (N=143)
Retatrutide 9 mg (N=143)
Retatrutide 12 mg (N=144)
Placebo (N=144)

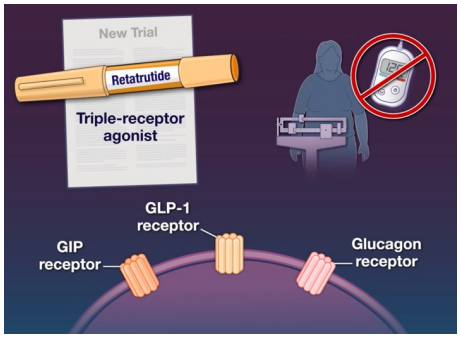

Death
1 adjudicated cardiovascular death in a participant with known heart failure 6 months after discontinuation of retatrutide
Number of Participants
0
1
2
3
4
5
6
0
3
1
2
Retatrutide 4 mg (N=584)
Retatrutide 9 mg (N=583)
Retatrutide 12 mg (N=582)
Placebo (N=586)

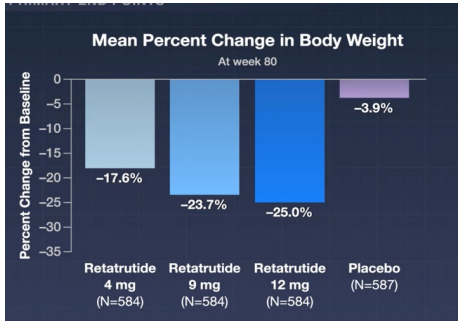

Medications that act through multiple mechanisms
Weight reduction
Health outcomes

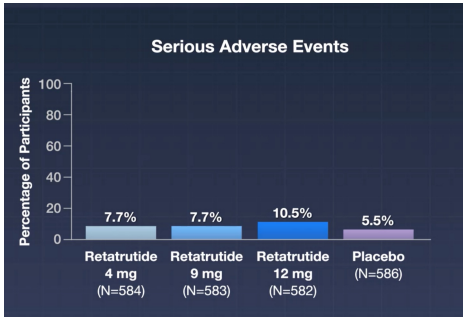

2339 Adults
Once weekly for 80 weeks
Retatrutide 4 mg
Retatrutide 9 mg
Retatrutide 12 mg
Placebo
Primary End Points
% change in body weight
Change in knee pain as noted by the WOMAC pain score in participants with knee osteoarthritis
Change in the apnea–hypopnea index in participants with obstructive sleep apnea
N=584
N=584
N=584
N=587


Change in Apnea–Hypopnea Index
At week 80
Number of Events per Hour
0
−10
−20
−30
−40
−22.9
−34.3
−31.7
−9.9
Retatrutide 4 mg (N=60)
Retatrutide 9 mg (N=61)
Retatrutide 12 mg (N=60)
Placebo (N=62)


Death
Remaining deaths were noncardiovascular or of undetermined cause
Number of Participants
0
1
2
3
4
5
6
0
3
1
2
Retatrutide 4 mg (N=584)
Retatrutide 9 mg (N=583)
Retatrutide 12 mg (N=582)
Placebo (N=586)


New Trial
Retatrutide
Triple-receptor agonist
GLP-1 receptor
GIP receptor
Glucagon receptor


Mean Percent Change in Body Weight
At week 80
Percent Change from Baseline
0
−5
−10
−15
−20
−25
−30
−35
−17.6%
−23.7%
−25.0%
−3.9%
Retatrutide 4 mg (N=584)
Retatrutide 9 mg (N=584)
Retatrutide 12 mg (N=584)
Placebo (N=587)


Serious Adverse Events
Percentage of Participants
100
80
60
40
20
0
7.7%
7.7%
10.5%
5.5%
Retatrutide 4 mg (N=584)
Retatrutide 9 mg (N=583)
Retatrutide 12 mg (N=582)
Placebo (N=586)


Retatrutide
Weight reduction
Reduced knee pain
Reduced apnea–hypopnea events

**CT-Koronarangiographie (auch CCTA oder Kardio-CT genannt)**

Im Gegensatz zur herkömmlichen Herzkatheteruntersuchung (invasive Koronarangiographie) müssen bei der CCTA **keine Schläuche (Katheter) über die Leiste oder das Handgelenk zum Herzen vorgeschoben werden**. Das Kontrastmittel wird stattdessen einfach über eine herkömmliche Venenkanüle am Arm verabreicht.

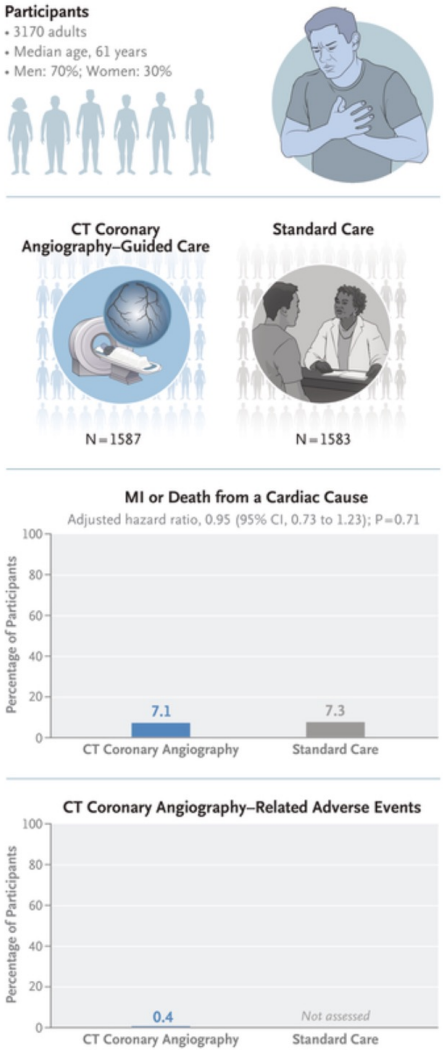


**Indikationen und Stärken**

- **Ausschluss einer KHK:** Die CCTA hat einen extrem hohen negativen Vorhersagewert (ca. 93 % bis 98 %). Das bedeutet: Ist der Befund unauffällig, kann eine Verengung der Herzkranzgefäße mit nahezu absoluter Sicherheit ausgeschlossen werden.
- **Abklärung von Symptomen:** Häufig eingesetzt bei unklaren Brustschmerzen (Angina Pectoris) und einem mittleren Risiko für Herzerkrankungen.
- **Früherkennung:** Sie kann im Gegensatz zu reinen Belastungstests auch weiche, noch nicht verkalkte Plaques in den Gefäßwänden darstellen.

# Targeted Use of Computed Tomographic Coronary Angiography in Acute Chest Pain

Many patients with suspected acute coronary syndrome in whom myocardial infarction has been ruled out in the emergency department remain at risk for cardiovascular events. Whether further investigation reduces this risk is unknown. In a multicenter, randomized, controlled trial, patients who presented to an emergency department in 14 hospitals across the United Kingdom were enrolled if myocardial infarction had been ruled out and high-sensitivity cardiac troponin testing indicated an intermediate risk of a cardiovascular event (maximum high-sensitivity cardiac troponin I or T concentration, >5 ng per liter). Participants were randomly assigned in a 1:1 ratio to receive either outpatient computed tomographic (CT) coronary angiography–guided care or standard care. The primary outcome was a composite of myocardial infarction or death from a cardiac cause.



Patients with very low troponin concentrations remain at low risk for myocardial infarction or death from a cardiac cause for up to 5 years. In contrast, those who are at intermediate risk according to high-sensitivity cardiac troponin testing are twice as likely as those with very low troponin concentrations to have coronary artery disease on computed tomographic (CT) coronary angiography and are 10 times as likely to have a subsequent myocardial infarction or die from a cardiac cause within 1 year after testing. Consequently, clinical practice guidelines recommend consideration of CT coronary angiography or noninvasive stress imaging in patients with suspected acute coronary syndrome who are at intermediate risk. However, the type of additional investigation that should be undertaken is unclear, and there is currently no evidence that any investigation alters clinical outcomes. We designed the present trial to determine whether performing early outpatient CT coronary angiography leads to a reduction in the risk of subsequent myocardial infarction or death from a cardiac cause among patients with suspected acute coronary syndrome but without myocardial infarction who are considered to be at intermediate risk.

**Trial Participants**

Adult patients (≥18 years of age) who presented to an emergency department or acute medical assessment center with suspected acute coronary syndrome were eligible for enrollment. Patients could be included if myocardial infarction had been ruled out but they were at intermediate risk for future myocardial infarction on the basis of a maximum high-sensitivity cardiac troponin I or T concentration between the low-risk threshold of 5 ng per liter and the sex-specific 99th percentile of the upper reference limit.

**Intervention and Procedures**

After providing consent, participants were randomly assigned in a 1:1 ratio to receive either CT coronary angiography–guided care plus standard care (CT coronary angiography group) or standard care alone (standard-care group).

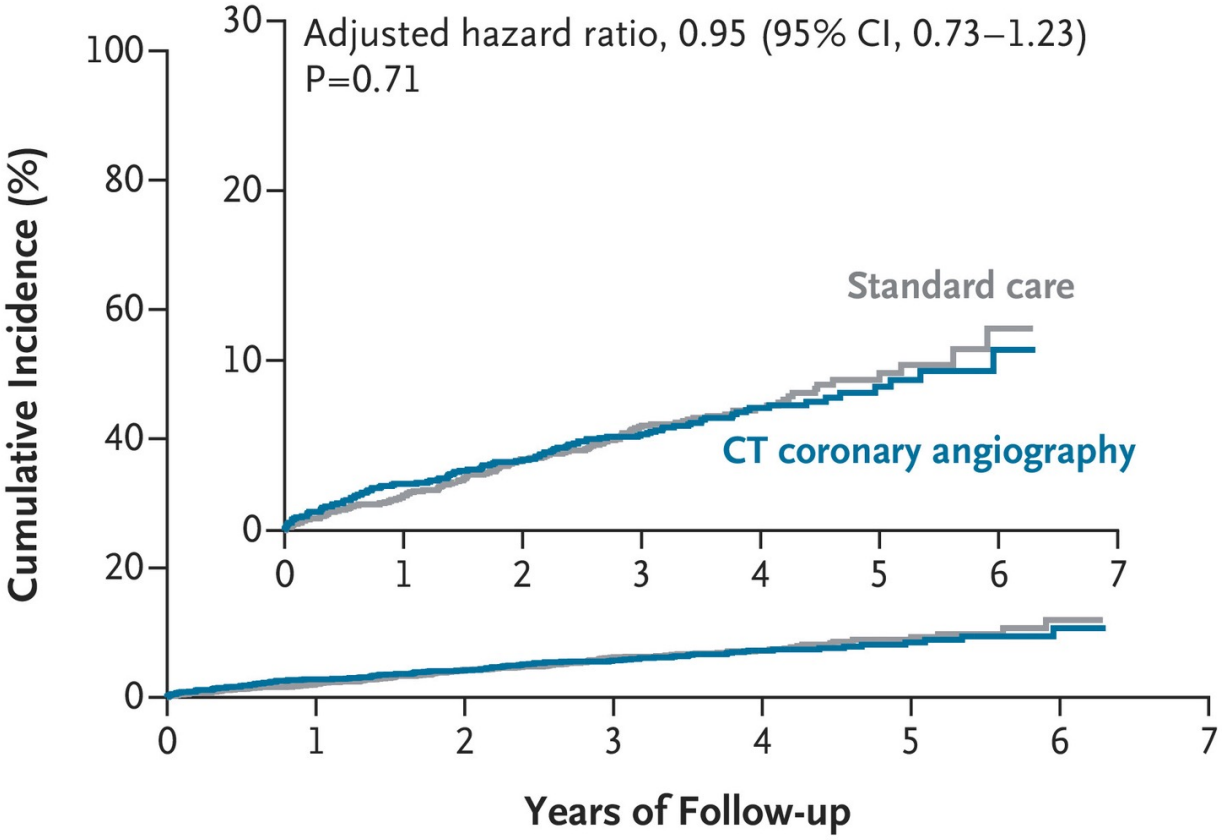
**Trial Outcomes**

Follow-up data were obtained from medical records at 90 days and annually thereafter and from participant questionnaires at 90 days and at 1 and 2 years. All the participants underwent follow-up until the minimum number of primary-outcome events had accrued. The primary outcome was a composite of myocardial infarction or death from a cardiac cause.

| Characteristic | CT Coronary Angiography (N=1587) | Standard Care (N=1583) |
|---|---|---|
| Median age (IQR) — yr | 61.0 (52.0–69.0) | 61.0 (53.0–70.0) |
| Female sex — no. (%) | 479 (30.2) | 477 (30.1) |
| Cardiovascular risk factors | | |
| Body-mass index† | 29.5±6.0 | 29.5±6.1 |
| Diabetes mellitus — no./total no. (%) | 237/1585 (15.0) | 216/1581 (13.7) |
| Hypertension — no./total no. (%) | 724/1585 (45.7) | 697/1581 (44.1) |
| Family history of coronary artery disease — no./total no. (%) | 626/1576 (39.7) | 545/1576 (34.6) |
| Current cigarette smoker — no./total no. (%) | 210/1584 (13.3) | 204/1581 (12.9) |
| Former smoker — no./total no. (%) | 606/1584 (38.3) | 605/1581 (38.3) |
| Medical history — no./total no. (%) | | |
| Previous myocardial infarction | 283/1585 (17.9) | 270/1581 (17.1) |
| Known angina | 236/1585 (14.9) | 242/1581 (15.3) |
| Coronary revascularization — no./total no. (%) | | |
| Previous percutaneous coronary intervention | 246/1584 (15.5) | 236/1581 (14.9) |
| Previous coronary-artery bypass grafting | 51/1585 (3.2) | 42/1581 (2.7) |
| Medications at randomization — no./total no. (%) | | |
| Antiplatelet therapy‡ | 452/1584 (28.5) | 469/1580 (29.7) |
| Statin | 689/1584 (43.5) | 684/1581 (43.3) |
| Preventative medication§ | 760/1584 (48.0) | 747/1581 (47.2) |
| ACE inhibitor or ARB | 610/1584 (38.5) | 557/1581 (35.2) |
| Beta-blocker | 384/1584 (24.2) | 372/1581 (23.5) |
| Chest discomfort at presentation — no./total no. (%) | 1397/1585 (88.1) | 1412/1581 (89.3) |
| Electrocardiogram — no./total no. (%) | | |
| Q waves | 52/1566 (3.3) | 52/1557 (3.3) |
| ST-segment elevation | 44/1564 (2.8) | 45/1556 (2.9) |
| ST-segment depression | 18/1563 (1.2) | 25/1556 (1.6) |
| T-wave inversion | 243/1566 (15.5) | 228/1557 (14.6) |
| Left or right bundle-branch block | 123/1564 (7.9) | 121/1557 (7.8) |
| Risk scores | | |
| Mean GRACE score¶ | 91±23 | 91±24 |
| GRACE score ≥109 — no./total no. (%)¶ | 722/1354 (53.3) | 700/1332 (52.6) |
| Mean HEART score‖ | 3.5±1.4 | 3.6±1.4 |
| HEART score >3 — no./total no. (%)‖ | 796/1576 (50.5) | 770/1576 (48.9) |
| Hematologic findings and clinical chemical variables | | |
| Hemoglobin — g/dl | 14.4±1.4 | 14.4±1.4 |
| Estimated glomerular filtration rate — ml/min | 63±10 | 63±10 |
| Median maximal high-sensitivity cardiac troponin I (IQR) — ng/liter | 8.0 (6.0–11.0) | 8.0 (6.0–11.0) |
| Median maximal high-sensitivity cardiac troponin T — ng/liter | 8.0 (7.0–10.0) | 8.0 (7.0–10.0) |

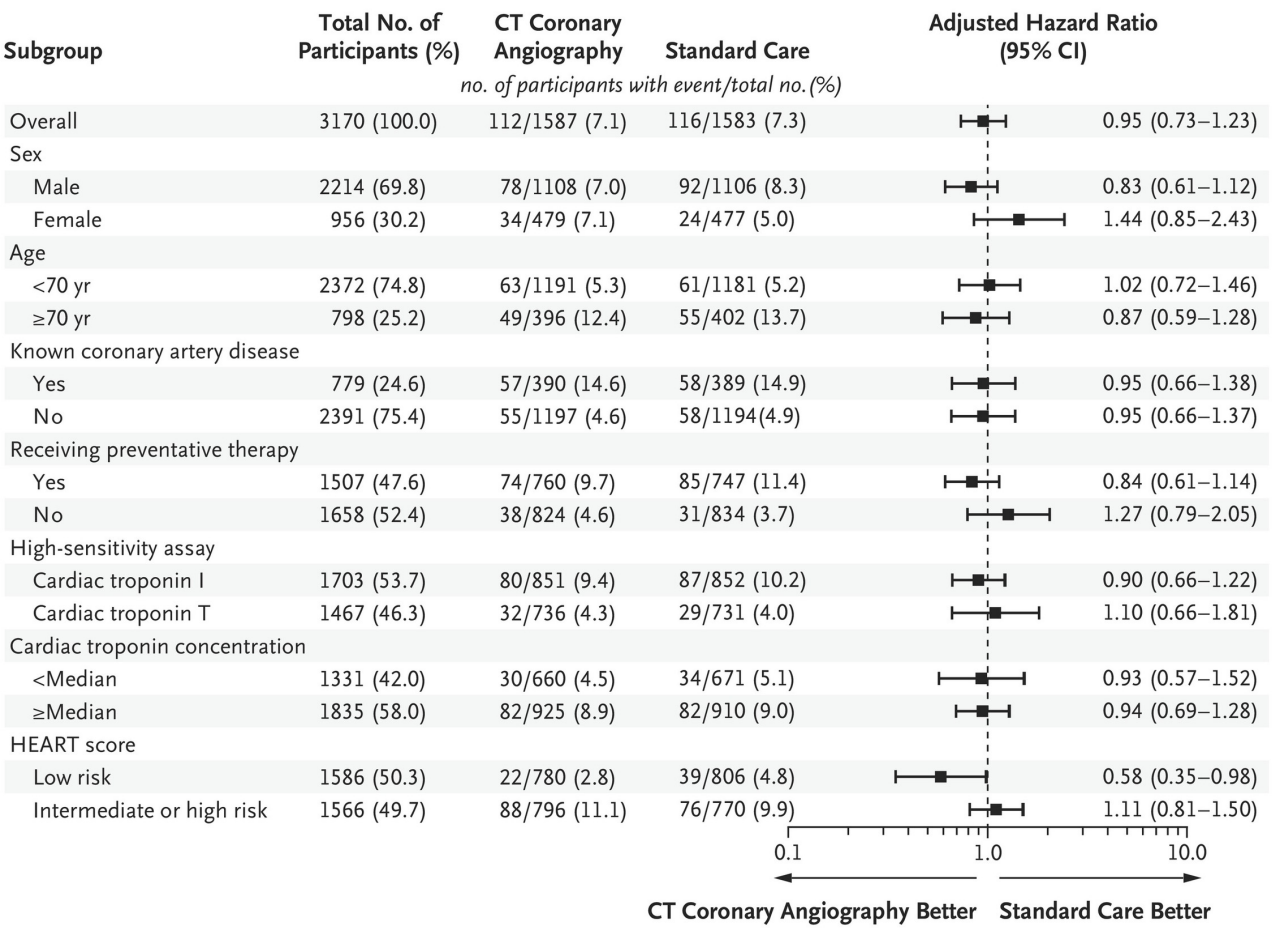
## Investigations and Care Management

| | CT Coronary Angiography (N=1587) | Standard Care (N=1583) |
|---|---|---|
| **CT coronary angiography** | | |
| Underwent as randomly assigned — no. (%) | 1462 (92.1) | — |
| Underwent although not randomly assigned — no. (%) | | |
| Within 90 days | — | 35 (2.2) |
| By the end of the trial | — | 103 (6.5) |
| Normal coronary arteries — no./total no. (%) | 465/1462 (31.8) | — |
| Coronary artery disease — no./total no. (%) | | |
| Nonobstructive | 622/1462 (42.5) | — |
| Obstructive | 331/1462 (22.6) | — |
| In proximal left anterior descending artery | 132/1462 (9.0) | — |
| In left main stem | 11/1462 (0.8) | — |
| One-vessel | 201/1462 (13.7) | — |
| Two-vessel | 87/1462 (6.0) | — |
| Three-vessel | 43/1462 (2.9) | — |
| Median CAD-RADS score (IQR)† | 2.0 (0.0–3.0) | — |
| Median segment involvement score (IQR)‡ | 2.0 (0.0–5.0) | — |
| Median segment stenosis score (IQR)§ | 2.0 (0.0–7.0) | — |
| CT coronary angiography was nondiagnostic or data were missing — no./total no. (%) | 44/1462 (3.0) | — |
| Noncardiac findings — no./total no. (%) | 617/1462 (42.2) | — |
| Clinically significant noncardiac findings — no./total no. (%) | 157/1462 (10.7) | — |
| **Other cardiac investigations — no. (%)** | | |
| Invasive coronary angiography | 177 (11.2) | 137 (8.7) |
| Noninvasive stress imaging | 133 (8.4) | 153 (9.7) |
| **Outpatient visit — no. (%)** | | |
| Cardiology at 90 days | 424 (26.7) | 264 (16.7) |
| Other specialty at 90 days | 91 (5.7) | 84 (5.3) |
| Cardiology at end of trial | 799 (50.3) | 598 (37.8) |
| **Medical therapy — no./total no. (%)** | | |
| Antiplatelet agent at 90 days¶ | 665/1568 (42.4) | 515/1568 (32.8) |
| Antiplatelet agent at end of trial¶ | 619/1492 (41.5) | 462/1462 (31.6) |
| Statin at 90 days | 994/1568 (63.4) | 760/1568 (48.5) |
| Statin at end of trial | 1024/1492 (68.6) | 813/1462 (55.6) |
| Preventative medication at 90 days‖ | 1046/1568 (66.7) | 820/1568 (52.3) |
| Preventative medication at end of trial‖ | 1070/1492 (71.7) | 854/1462 (58.4) |
| **Coronary revascularization — no. (%)** | | |
| PCI or CABG | | |
| At 90 days | 26 (1.6) | 15 (0.9) |
| At end of trial | 98 (6.2) | 77 (4.9) |



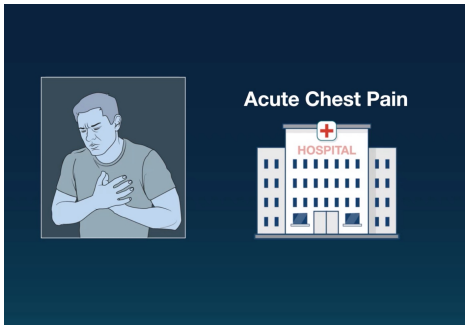

**Incidence of Myocardial Infarction or Death from a Cardiac Cause.**

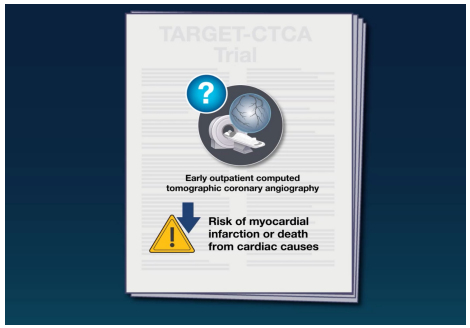
Shown are Kaplan–Meier survival curves for the incidence of myocardial infarction or death from a cardiac cause (the composite primary outcome) among patients assigned to receive either computed tomographic (CT) coronary angiography–guided care or standard care. The inset shows the same data on an expanded y axis.

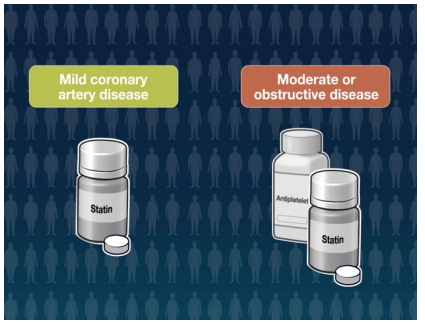



**Incidence of Myocardial Infarction or Death from a Cardiac Cause in Prespecified Subgroups.**

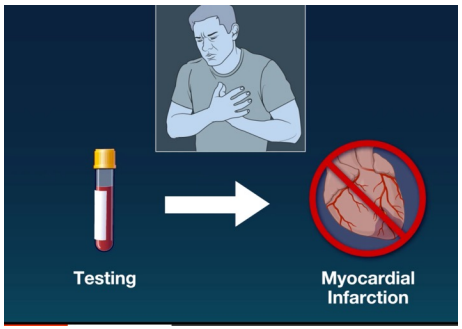
Shown is a forest plot of the incidence of myocardial infarction or death from a cardiac cause (the composite primary outcome) among patients assigned to receive either CT coronary angiography–guided care or standard care, with stratification according to prespecified subgroups. Preventative therapy included any antiplatelet agent or statin received at randomization. Cardiac troponin concentration reflects sex- and assay-specific median maximum cardiac troponin concentrations. The History, Electrocardiogram, Age, Risk Factors, and Troponin (HEART) score ranges from 0 to 10, with scores of 3 or lower indicating low risk and scores higher than 3 indicating intermediate or high risk.

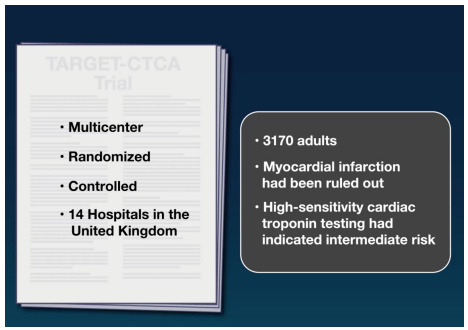

Acute Chest Pain
HOSPITAL

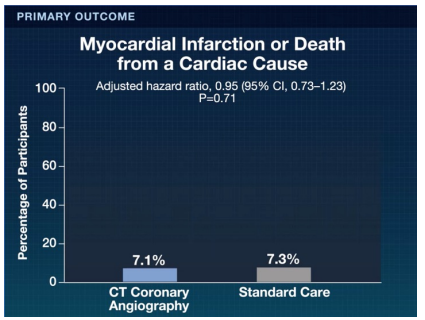

TARGET-CTCA Trial
Early outpatient computed tomographic coronary angiography
Risk of myocardial infarction or death from cardiac causes

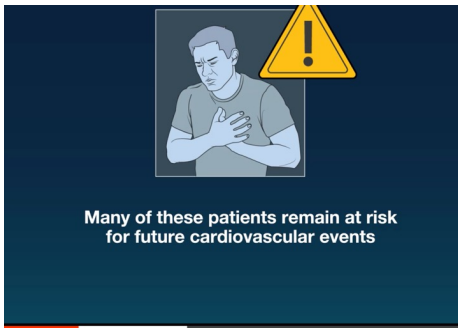

Mild coronary artery disease
Moderate or obstructive disease
Statin
Antiplatelet
Statin

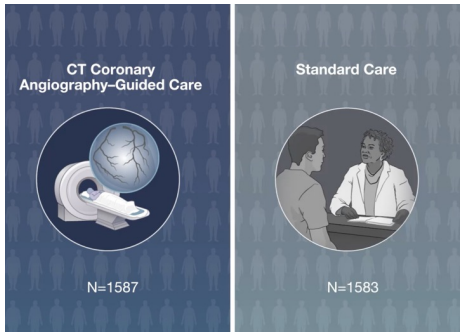

Did not result in a lower incidence of subsequent myocardial infarction or death from a cardiac cause than standard care

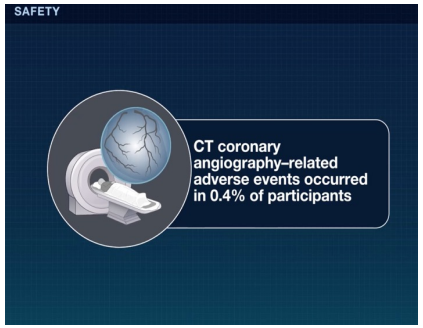

Testing
Myocardial Infarction


TARGET-CTCA Trial
• Multicenter
• Randomized
• Controlled
• 14 Hospitals in the United Kingdom
• 3170 adults
• Myocardial infarction had been ruled out
• High-sensitivity cardiac troponin testing had indicated intermediate risk


PRIMARY OUTCOME
Myocardial Infarction or Death from a Cardiac Cause
Adjusted hazard ratio, 0.95 (95% CI, 0.73–1.23)
P=0.71
Percentage of Participants
100
80
60
40
20
0
7.1%
7.3%
CT Coronary Angiography
Standard Care


Many of these patients remain at risk for future cardiovascular events


CT Coronary Angiography–Guided Care
N=1587
Standard Care
N=1583

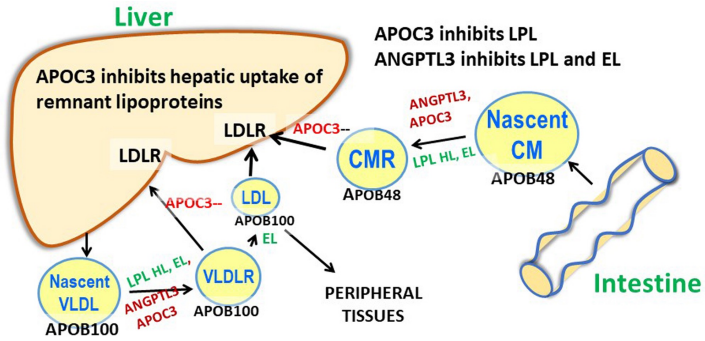

SAFETY
CT coronary angiography–related adverse events occurred in 0.4% of participants

**Apolipoprotein C3 (kurz ApoC3 oder APOC3)** ist ein regulatorisches Protein im menschlichen Körper, das eine zentrale Rolle im Fettstoffwechsel spielt und in der modernen Medizin ein wichtiges therapeutisches Ziel zur Senkung extrem hoher Triglyceridwerte darstellt. Es wird hauptsächlich in der Leber und im Dünndarm gebildet und reist im Blut auf der Oberfläche bestimmter Fett-Transportpartikel (Lipoproteine) wie VLDL und Chylomikronen mit.

## Funktion im Körper

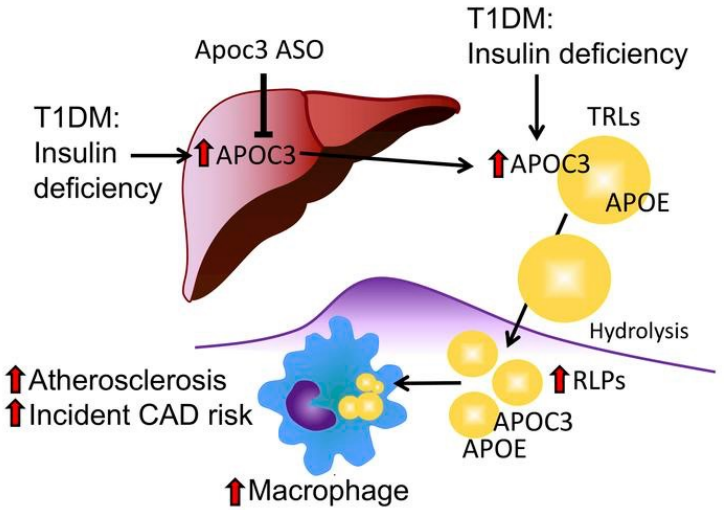
Die Hauptaufgabe von ApoC3 besteht darin, den Abbau von Triglyceriden (Fetten) im Blut zu bremsen. Dies geschieht über zwei Wege:

- **Enzym-Hemmung:** Es blockiert die *Lipoproteinlipase* (LPL) – das wichtigste Enzym, das Fette im Blut aufspaltet, damit die Zellen sie als Energie nutzen oder speichern können.
- **Verzögerte Ausscheidung:** Es verhindert, dass die Leber verbleibende Fettpartikel (Remnants) zügig aus dem Blutkreislauf filtert und abbaut.




**Inhibiting ANGPTL3 increases TG lipolysis and TRL remnant removal in the presence of LPL. Inhibiting ANGPTL3 increases LDL uptake in the absence of LDL receptors**

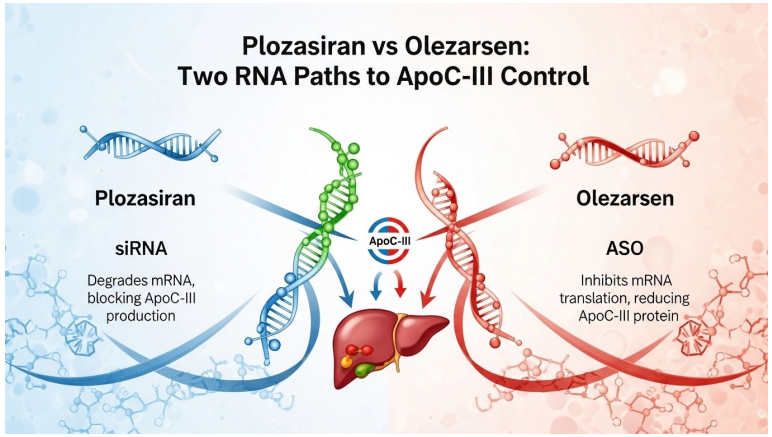
**Inhibiting APOC3 increases TG lipolysis in the presence of LPL and increases TRL remnant clearance particularly in the absence of LPL**



**Plozasiran** ist ein innovativer, RNA-basierter Arzneistoff (siRNA) zur Senkung von Blutfetten.

## Wichtigste Eigenschaften und Wirkung

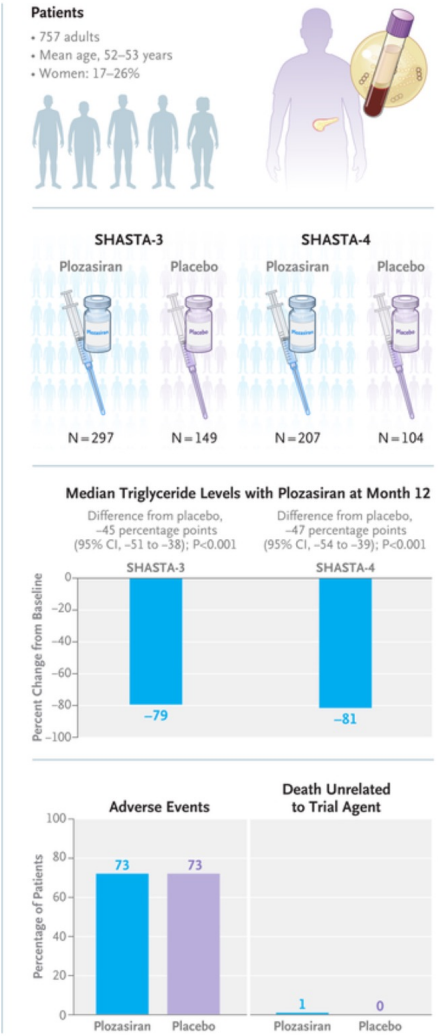
- **Wirkmechanismus:** Es handelt sich um eine doppelsträngige siRNA, die gezielt die Bildung des Proteins *Apolipoprotein C-III* (ApoC-III) in der Leber über RNA-Interferenz unterdrückt.
- **Funktion:** ApoC-III wirkt normalerweise als „Bremse“ beim Abbau von Triglyceriden (Blutfetten). Durch das Hemmen des Proteins kann der Körper Triglyceride deutlich schneller abbauen und aus dem Blut entfernen.
- **Anwendung:** Das Medikament wird als subkutane Injektion (unter die Haut, z. B. am Bauch oder Oberschenkel) verabreicht.
- **Dosierung:** Die empfohlene Dosis beträgt **25 mg alle 3 Monate** (nach Anleitung auch zur Selbstinjektion geeignet)




- **Das Transportsystem:** Die siRNA ist an ein Zuckermolekül namens **GalNAc** (*N-Acetylgalactosamin*) gekoppelt.
- **Die Funktion:** Dieser GalNAc-Komplex dient als biologischer „Vektor“ bzw. Wegweiser. Er sorgt dafür, dass der Wirkstoff nach der Spritze unter die Haut gezielt und fast ausschließlich von den **Leberzellen (Hepatozyten)** aufgenommen wird.

# Plozasiran for Severe Hypertriglyceridemia and Risk of Pancreatitis

Severe hypertriglyceridemia is associated with an increased risk of acute pancreatitis. Plozasiran, a small interfering RNA targeting *APOC3* messenger RNA, lowers triglyceride levels and potentially mitigates the risk of acute pancreatitis.
In two double-blind, placebo-controlled trials, 757 adults with severe hypertriglyceridemia were randomly assigned in a 2:1 ratio to receive plozasiran (25 mg) or placebo at baseline and at months 3, 6, and 9. These trials had identical designs, end points, and analytic plans. The primary end point was the percent change in the fasting plasma triglyceride level from baseline to month 12. Key secondary end points were the percent change in the fasting triglyceride level from baseline to month 10, a fasting triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter) and less than 150 mg per deciliter (1.7 mmol per liter), the percent change in the fasting serum triglyceride level at month 12 for patients with a baseline triglyceride level of 880 mg per deciliter or greater, and changes in remnant cholesterol and non–HDL cholesterol. A pooled analysis addressed adjudicated acute pancreatitis, incidence, and first-event timing.



Apolipoprotein C-III (APOC3) is a key inhibitor of lipoprotein lipase that regulates triglyceride-rich lipoprotein metabolism. Lipoprotein lipase and hepatic receptors mediate clearance of lipoproteins from the circulation. Genetic deficiency of APOC3 is associated with lower triglyceride levels and reduced cardiometabolic risk. Plozasiran is a hepatocyte-targeted, N-acetylgalactosamine–conjugated small interfering RNA that reduces APOC3 synthesis and lowers triglyceride levels through lipoprotein lipase–dependent and –independent mechanisms. Plozasiran has been shown to lower the risks of hypertriglyceridemia and pancreatitis that are caused by familial chylomicronemia syndrome, a condition that is defined both genetically and clinically. However, data are needed on the ability of plozasiran to lower triglyceride levels and mitigate the risk of acute pancreatitis in adult patients with severe hypertriglyceridemia, a population that is larger and more clinically heterogeneous than the patients with the familial syndrome.

**Trial Population**

Adults (≥18 years of age) with established severe hypertriglyceridemia were eligible for participation. The key inclusion criteria were a documented history of a fasting triglyceride level of at least 500 mg per deciliter (≥5.6 mmol per liter), confirmed by a mean of two consecutive fasting measurements obtained during a screening period of up to 8 weeks, and a screening glycated hemoglobin level of less than 9.0%. Patients received standard background lipid-lowering therapy in accordance with local clinical guidelines unless unacceptable side effects were documented.

**Randomization and Treatment**

The patients were randomly assigned in a 2:1 ratio to receive subcutaneous plozasiran (25 mg) or matching placebo. The double-blind treatment period lasted 12 months, during which time four doses were administered at 3-month intervals. After month 12, patients were enrolled in an optional open-label extension study (a separate protocol) or underwent a follow-up assessment 3 months after the end of treatment.

**End Points**

First, the percent change from baseline in the fasting serum triglyceride level at month 12, as compared with placebo (primary efficacy end point); second, the percent change from baseline in the triglyceride level at month 10, as compared with placebo.

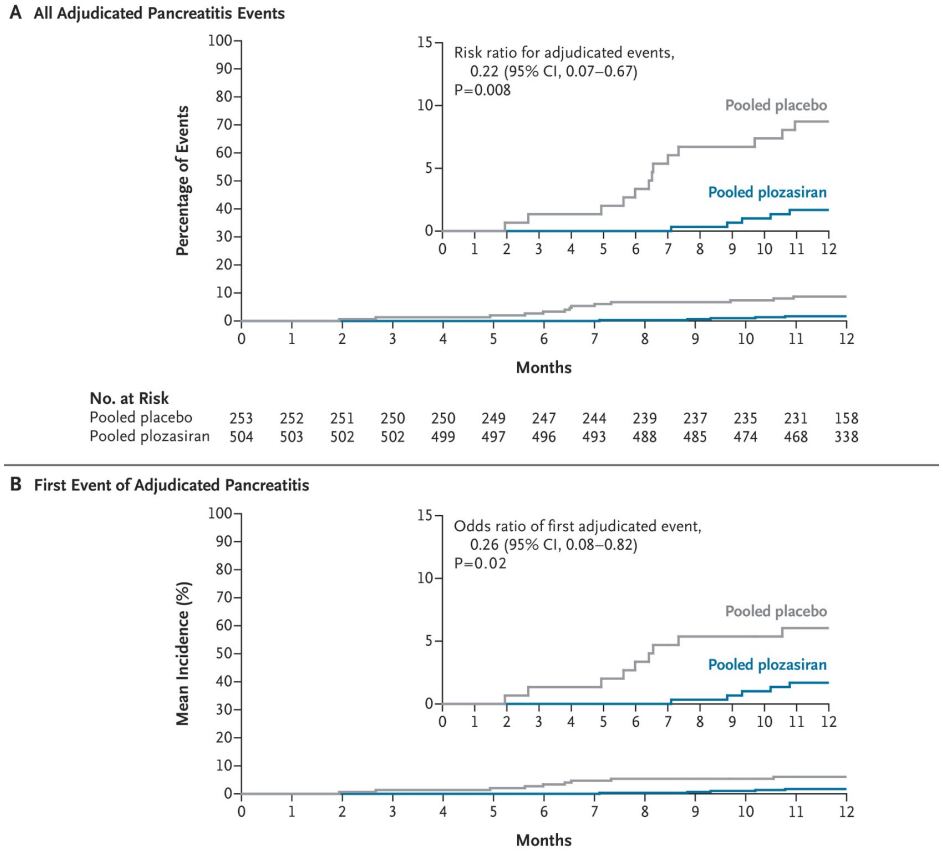
| Characteristic | SHASTA-3 | | SHASTA-4 | |
|---|---|---|---|---|
| | Plozasiran (N=297) | Placebo (N=149) | Plozasiran (N=207) | Placebo (N=104) |
| **Demographic** | | | | |
| Age — yr | 52±12 | 51±12 | 53±11 | 53±12 |
| Male sex at birth — no. (%) | 247 (83) | 122 (82) | 160 (77) | 69 (66) |
| Race — no. (%)† | | | | |
| White | 223 (75) | 109 (73) | 184 (89) | 87 (84) |
| Asian | 62 (21) | 38 (26) | 9 (4) | 9 (9) |
| Black | 3 (1) | 0 | 13 (6) | 3 (3) |
| Hispanic ethnic group — no. (%) | 57 (19) | 33 (22) | 39 (19) | 21 (20) |
| **Medical history** | | | | |
| Body-mass index‡ | 31±5.3 | 30±4.8 | 32±4.9 | 31±5.4 |
| Metabolic syndrome — no. (%) | 4 (1) | 3 (2) | 4 (2) | 1 (1) |
| Cardiovascular disease — no. (%) | 104 (35) | 37 (25) | 68 (33) | 35 (34) |
| Hypertension — no. (%) | 187 (63) | 92 (62) | 147 (71) | 71 (68) |
| Diabetes mellitus — no. (%) | 174 (59) | 81 (54) | 130 (63) | 57 (55) |
| Acute pancreatitis — no. (%) | | | | |
| Any | 57 (19) | 37 (25) | 45 (22) | 21 (20) |
| Within 5 yr | 33 (11) | 21 (14) | 27 (13) | 14 (13) |
| **Laboratory measures** | | | | |
| Triglycerides | | | | |
| Median (IQR) — mg/dl | 663 (537–956) | 674 (545–979) | 737 (566–1108) | 704 (558–1076) |
| Mean — mg/dl | 835±504 | 827±512 | 956±657 | 939±683 |
| Plasma value ≥880 mg/dl — no. (%) | 91 (31) | 44 (30) | 77 (37) | 38 (37) |
| Apolipoprotein — mg/dl | | | | |
| C-III | 33±15 | 31±15 | 37±17 | 35±18 |
| B | 98±28 | 96±27 | 99±27 | 99±27 |
| Cholesterol — mg/dl | | | | |
| Total | 206±69 | 205±80 | 221.5±81.4 | 223.5±94.9 |
| Remnant | 108±64 | 109±80 | 131±84 | 131±97 |
| Non–high-density lipoprotein | 177±69 | 176±81 | 194±82 | 195±96 |
| High-density lipoprotein | 29±10 | 29±12 | 28±10 | 29±12 |
| Low-density lipoprotein: UC | 68±33 | 67±33 | 62±32 | 64±34 |
| Other | | | | |
| Glycated hemoglobin — %§ | 6.4±1.1 | 6.4±1.1 | 6.6±1.2 | 6.4±1.1 |

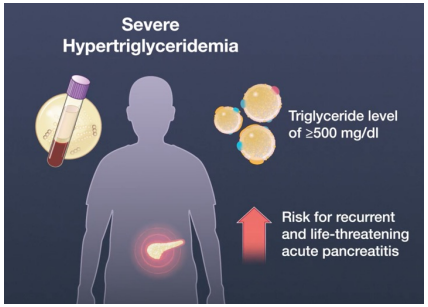
# Efficacy

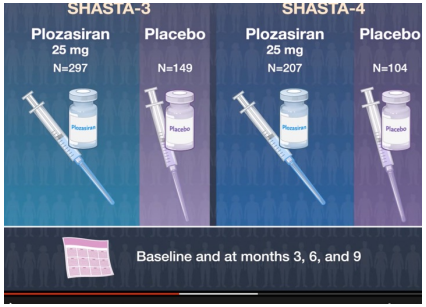
| Measure | SHASTA-3 | | SHASTA-4 | |
|---|---|---|---|---|
| | Plozasiran (N=297) | Placebo (N=149) | Plozasiran (N=207) | Placebo (N=104) |
| **Triglycerides** | | | | |
| Median level at baseline (IQR) — mg/dl | 663 (537 to 956) | 674 (545 to 979) | 737 (566 to 1108) | 704 (558 to 1076) |
| Median level at 12 mo (IQR) — mg/dl | 142 (101 to 233) | 489 (316 to 767) | 141 (101 to 241) | 500 (335 to 892) |
| Median change from baseline (IQR) — mg/dl | −500 (−783 to −333) | −158 (−342 to 35) | −551 (−845 to −393) | −192 (−421 to 2.9) |
| Median percent change from baseline (IQR) | −79 (−85 to −65) | −28 (−50 to 5.3) | −81 (−88 to −68) | −27 (−50 to 0.4) |
| Estimated difference from placebo (95% CI) — percentage points†‡ | −45 (−51 to −38) | — | −47 (−54 to −39) | — |
| Median level at month 10 (IQR) — mg/dl | 104 (77 to 164) | 525 (290 to 881) | 107 (78 to 167) | 505 (355 to 781) |
| Median change from baseline (IQR) — mg/dl | −546 (−822 to −393) | −144 (−348 to 106) | −605 (−893 to −426) | −194 (−422 to 11) |
| Median percent change from baseline (IQR) | −84 (−90 to −75) | −19 (−53 to 12) | −85 (−90 to −76) | −26 (−48 to 2) |
| Estimated difference from placebo (95% CI) — percentage points†‡ | −55 (−63 to −46) | — | −53 (−61 to −45) | — |
| **Patients with triglyceride level <500 mg/dl at month 12** | | | | |
| No. of patients/total no. (%) | 255/279 (91) | 71/140 (51) | 175/189 (93) | 49/98 (50) |
| Risk difference vs. placebo (95% CI)†‡ | 0.4 (0.3 to 0.5) | — | 0.4 (0.3 to 0.5) | — |
| **Patients with triglyceride level <150 mg/dl at month 12** | | | | |
| No. of patients/total no. (%) | 146/279 (52) | 11/140 (8) | 104/189 (55) | 2/98 (2) |
| Risk difference vs. placebo (95% CI)†‡ | 0.4 (0.3 to 0.5) | — | 0.5 (0.4 to 0.6) | — |
| **Triglyceride level ≥880 mg/dl at baseline** | | | | |
| No. of patients | 91 | 44 | 77 | 38 |
| Median triglyceride level at baseline (IQR) — mg/dl | 1241 (1036 to 1559) | 1258 (1062 to 1499) | 1259 (1042 to 1821) | 1154 (1023 to 1686) |
| Median triglyceride level at month 12 (IQR) — mg/dl | 193 (115 to 420) | 776 (456 to 1362) | 215 (127 to 342) | 878 (511 to 1988) |
| Median change from baseline (IQR) — mg/dl | −955 (−1243 to −794) | −372 (−978 to 101) | −1072 (−1612 to −816) | −421 (−791 to 47) |
| Median percent change from baseline (IQR) — percentage points | −85 (−91 to −73) | −38 (−70 to 8.0) | −85 (−91 to −75) | −25 (−60 to 4) |
| Least-squares mean difference from placebo (95% CI) — percentage points†‡ | −42 (−58 to −26) | — | −47 (−62 to −32) | — |
| **Remnant cholesterol** | | | | |
| Level at baseline — mg/dl | 108±64 | 109±80 | 131±84 | 131±97 |
| Level at month 12 — mg/dl | 33±29 | 94±84 | 35±34 | 111±91 |
| Change from baseline — mg/dl | −75±62 | −16±87 | −97±81 | −19±93 |
| Least-squares mean percent change from baseline (95% CI) | −51 (−61 to −40) | 2.7 (−8.9 to 14) | −49 (−59 to −39) | 7.6 (−4.4 to 20) |
| Least-squares mean difference from placebo (95% CI) — percentage points†‡ | −53 (−65 to −42) | — | −56 (−69 to −44) | — |
| **Non-HDL cholesterol** | | | | |
| Level at baseline — mg/dl | 177±69 | 176±81 | 194±82 | 194±95 |
| Level at month 12 — mg/dl | 126±53 | 167±85 | 119±51 | 177±92 |
| Change from baseline — mg/dl | −51±73 | −11±85 | −75±79 | −16±93 |
| Least-squares mean percent change from baseline (95% CI) | −17 (−23 to −11) | 3.4 (−3.8 to 11) | −24 (−31 to −19) | 3.9 (−4.7 to 12) |
| Least-squares mean difference from placebo (95% CI) — percentage points†‡ | −21 (−28 to −13) | — | −28 (−37 to −19) | — |

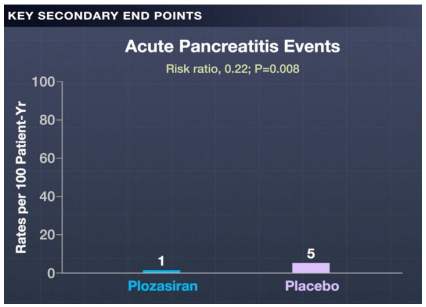
# Adveerse

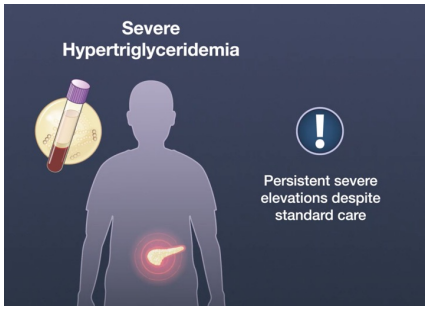
| Event | Pooled Plozasiran (N=504) | Pooled Placebo (N=252) | Total (N=756) |
|---|---|---|---|
| | *number of patients (percent)* | | |
| Any adverse event | 368 (73) | 184 (73) | 552 (73) |
| Most common adverse events reported in ≥5% of patients in either group | | | |
| Worsening of glycemic control† | 72 (14) | 22 (9) | 94 (12) |
| Diarrhea | 28 (6) | 8 (3) | 36 (5) |
| Abdominal pain | 13 (3) | 17 (7) | 30 (4) |
| Serious adverse event | 42 (8) | 24 (10) | 66 (9) |
| Maximum severity | | | |
| Mild | 91 (18) | 50 (20) | 141 (19) |
| Moderate | 227 (45) | 106 (42) | 333 (44) |
| Severe | 42 (8) | 26 (10) | 68 (9) |
| Death‡ | 3 (1) | 0 | 3 (<1) |
| Leading to discontinuation of plozasiran or placebo | 7 (1) | 2 (1) | 9 (1) |
| Injection-site reaction§ | 16 (3) | 5 (2) | 21 (3) |
| Decrease in platelet count | 2 (<1) | 4 (2) | 6 (1) |
| Hypersensitivity | 1 (<1) | 1 (<1) | 2 (<1) |
| Increase in ALT or AST level at any postbaseline visit | | | |
| ≥3× ULN | 5 (1) | 4 (2) | 9 (1) |
| ≥5× ULN | 2 (<1) | 2 (1) | 4 (<1) |

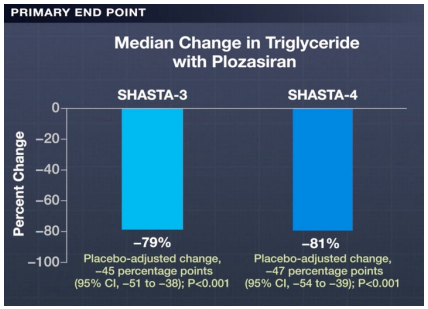


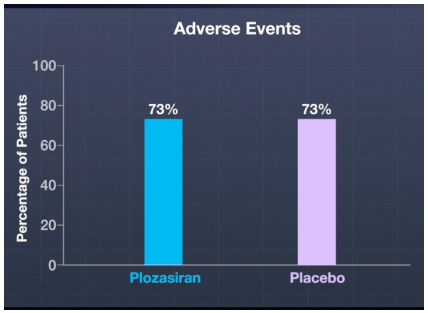

Severe
Hypertriglyceridemia
Triglyceride level of ≥500 mg/dl
Risk for recurrent and life-threatening acute pancreatitis

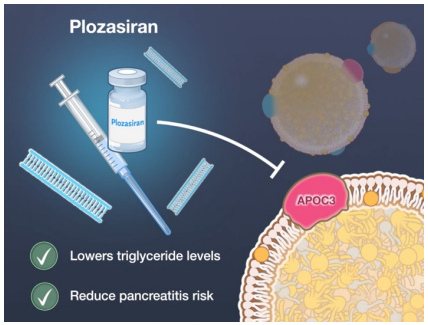

SHASTA-3
SHASTA-4
Plozasiran 25 mg
N=297
Placebo
N=149
Plozasiran 25 mg
N=207
Placebo
N=104
Baseline and at months 3, 6, and 9

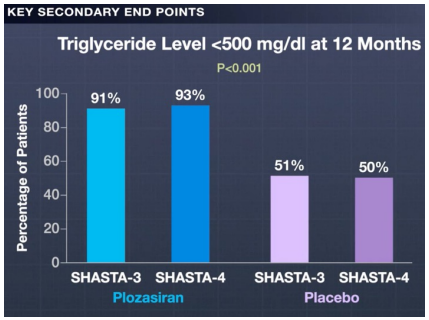

KEY SECONDARY END POINTS
Acute Pancreatitis Events
Risk ratio, 0.22; P=0.008
Rates per 100 Patient-Yr
100
80
60
40
20
0
1
5
Plozasiran
Placebo

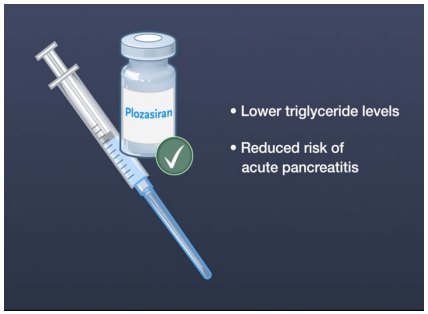

Severe
Hypertriglyceridemia
Persistent severe elevations despite standard care


PRIMARY END POINT
Median Change in Triglyceride with Plozasiran
SHASTA-3
SHASTA-4
Percent Change
0
−20
−40
−60
−80
−100
−79%
Placebo-adjusted change, −45 percentage points (95% CI, −51 to −38); P<0.001
−81%
Placebo-adjusted change, −47 percentage points (95% CI, −54 to −39); P<0.001

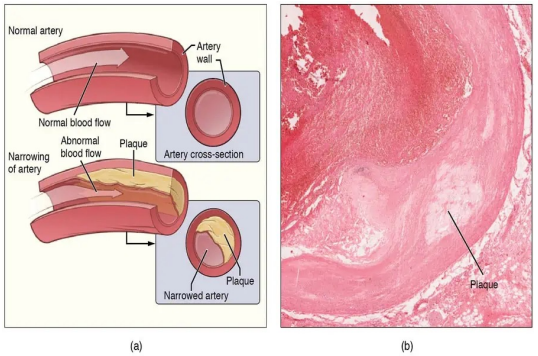

Adverse Events
Percentage of Patients
100
80
60
40
20
0
73%
73%
Plozasiran
Placebo

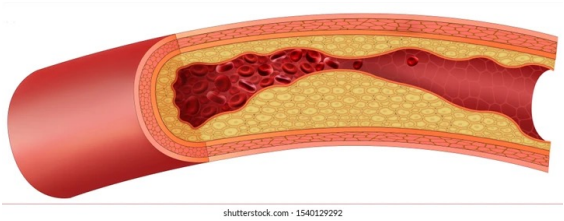

Plozasiran
APOC3
Lowers triglyceride levels
Reduce pancreatitis risk

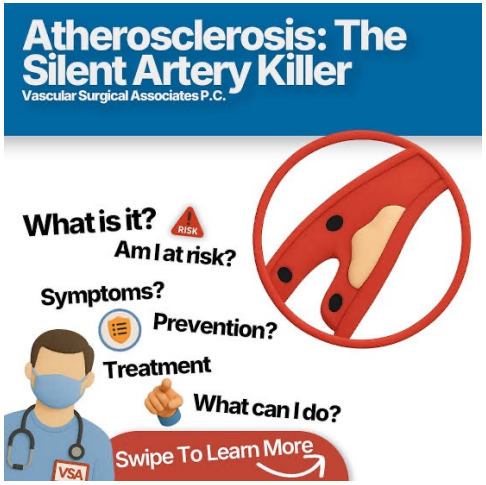

KEY SECONDARY END POINTS
Triglyceride Level <500 mg/dl at 12 Months
P<0.001
Percentage of Patients
100
80
60
40
20
0
91%
93%
51%
50%
SHASTA-3
SHASTA-4
SHASTA-3
SHASTA-4
Plozasiran
Placebo


Plozasiran
• Lower triglyceride levels
• Reduced risk of acute pancreatitis

**Stille (oder asymptomatische) Arteriosklerose** bezeichnet die Einlagerung von Fett, Cholesterin, Kalzium und Entzündungszellen in den Arterienwänden (Plaques), ohne dass dabei spürbare Symptome oder kardiovaskuläre Ereignisse (wie Herzinfarkt oder Schlaganfall) auftreten.




## Wichtigste Erkenntnisse zur stillen Arteriosklerose

- **Hohe Verbreitung:** Aktuelle Studiendaten (wie die REACT-Initiative) zeigen, dass eine stille Arteriosklerose weit verbreitet ist. Insgesamt sind rund **57,1 %** der Erwachsenen ohne bekannte Herzkrankheit betroffen.

- **Früher Beginn:** Plaque-Bildung kann bereits in jungen Jahren auftreten. Bei 18- bis 29-Jährigen liegt die Prävalenz bei etwa 8,7 % (Männer) und 6,7 % (Frauen). Mit zunehmendem Alter steigt der Anteil stark an und erreicht bei 60- bis 70-Jährigen rund **90 %**.

- **Geschlechtsspezifischer Verlauf:** Männer entwickeln die Veränderungen im Schnitt 5 bis 10 Jahre früher; Frauen zeigen in den Wechseljahren bzw. im mittleren Lebensalter einen steileren Anstieg.

- **Lücke in der Risikoabschätzung:** Herkömmliche Risikorechner (wie SCORE2) stufen viele Betroffene fälschlicherweise als „geringes Risiko“ ein, weil sie die bereits vorhandene subklinische Plaque-Last im Gefäßbild nicht erfassen.

# Prevalence of Silent Atherosclerosis across Adult Life

Atherosclerosis may begin in early adulthood and remain clinically silent for decades before cardiovascular disease manifests. Although silent atherosclerosis is associated with cardiovascular events and death independent of traditional cardiovascular disease risk factors, its age- and sex-specific prevalence, vascular territory distribution, and plaque volume across adult life remain incompletely defined.

**Methods**

We conducted a prospective cohort study in Denmark and Spain. Adults 18 to 70 years of age without known atherosclerotic cardiovascular disease were enrolled in five prespecified age strata that included balanced numbers of women and men. Silent atherosclerosis was assessed at baseline with three-dimensional vascular ultrasonography of the carotid and femoral arteries and with coronary computed tomographic angiography.

**Conclusions**

This study of silent atherosclerosis showed that the disease was detectable in early adulthood, with age- and sex-associated increases in prevalence across arterial territories and marked increases in plaque volume.

The epidemiologic characteristics of silent atherosclerosis across adult life remain incompletely defined. Most large imaging cohorts have enrolled participants who were middle aged and older, whereas studies involving adults younger than 40 years of age have often been small, limited to selected populations, or based on surrogate markers rather than direct quantification of plaque. As a result, there is no clear age- and sex-specific atlas to show when atherosclerosis is already present, where it is distributed, and differences in the accumulation of atherosclerosis in a cross-sectional cohort from early adulthood through later adult life.

The REACT Initiative was designed to address this gap. We systematically assessed silent atherosclerosis in adults 18 to 70 years of age without known clinical atherosclerotic cardiovascular disease, using standardized multimodal imaging of the carotid, femoral, and coronary arteries together with comprehensive clinical and biologic phenotyping. Here, we report the baseline age- and sex-specific prevalence, vascular distribution, and plaque volume across adult life, and examine the extent to which conventional cardiovascular risk assessment identifies participants with established but clinically silent atherosclerosis.

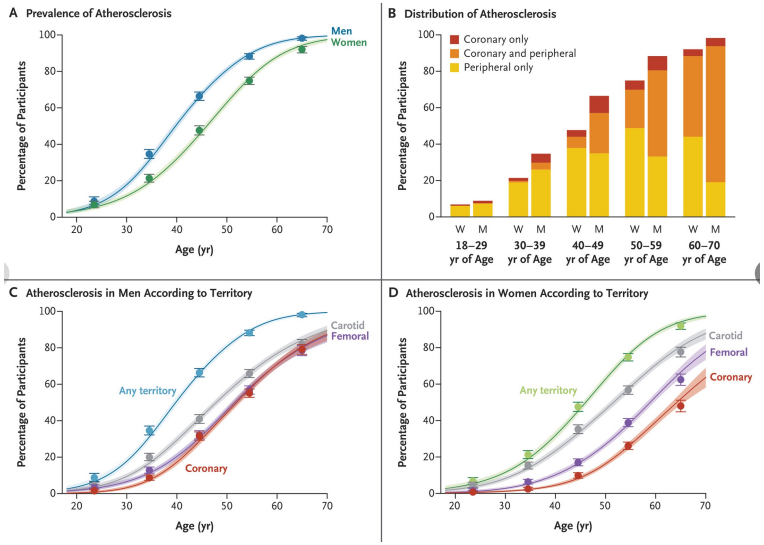
**Study Participants and Assessments**

Adults 18 to 70 years of age were eligible if they had no history of established clinical atherosclerotic cardiovascular disease (e.g., myocardial infarction, ischemic stroke, or peripheral artery disease) or previous coronary revascularization. Symptoms such as angina or claudication in the absence of established clinical atherosclerotic cardiovascular disease were not formally reasons for exclusion. Enrollment was designed a priori to include approximately 2000 participants each in the 18-to-29–years and 60-to-70–years age strata and approximately 4000 participants each in the 30-to-39–years, 40-to-49–years, and 50-to-59–years age strata, with balance according to country and sex within each stratum. Participants underwent multimodal imaging for silent atherosclerosis in the carotid, femoral, and coronary arteries. Carotid and femoral atherosclerosis was assessed with three-dimensional vascular ultrasound. Coronary atherosclerosis was assessed with coronary CT angiography, and coronary calcification with noncontrast CT. Cardiovascular risk was estimated with the use of the Systematic Coronary Risk Evaluation 2 (SCORE2) framework, which predicts the 10-year risk of fatal and nonfatal cardiovascular disease in European persons 40 to 69 years of age, with higher scores indicating higher risk.

**Outcomes**

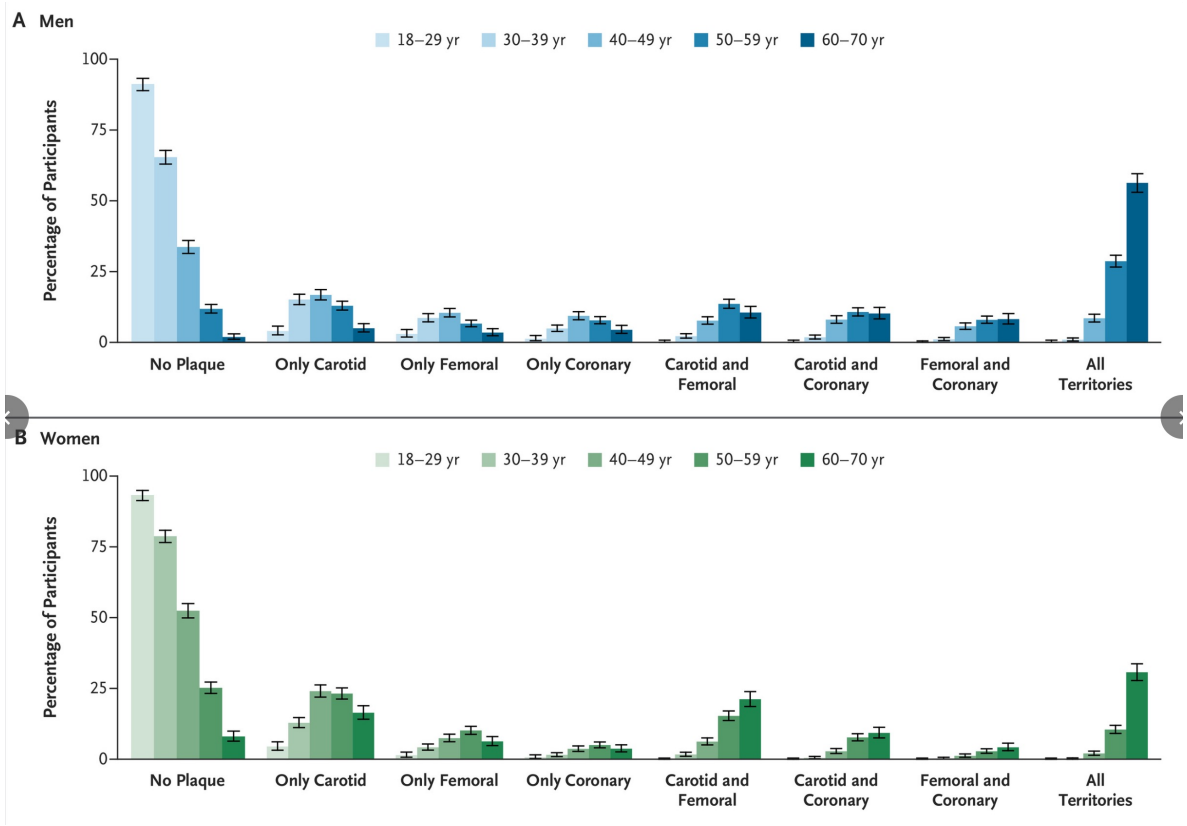
The primary outcome was the presence of silent atherosclerosis, defined as plaque in at least one examined vascular territory. Key secondary outcomes were the presence of plaque in each vascular territory, plaque volume in each territory, global peripheral plaque volume, coronary plaque volume, and coronary-artery–calcium score.

| Characteristic | Overall Population | | Men | | | | | | Women | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All | Effect Est. (95% CI) | 18–29 yr (N=982) | 30–39 yr (N=1917) | 40–49 yr (N=2105) | 50–59 yr (N=2124) | 60–70 yr (N=1037) | Effect Est. (95% CI) | 18–29 yr (N=1233) | 30–39 yr (N=1957) | 40–49 yr (N=2040) | 50–59 yr (N=2247) | 60–70 yr (N=1166) | Effect Est. (95% CI) |
| Age — yr | 45.0± 12.5 | −0.19 (−0.57 to 0.19) | 24.5± 3.2 | 35.3± 2.8 | 44.9± 2.9 | 54.2± 2.9 | 64.1± 3.0 | — | 24.5± 3.2 | 35.3± 2.9 | 45.1± 2.9 | 54.2± 2.8 | 64.1± 3.0 | — |
| Spain — no. (%)† | 8462 (50.3) | — | 496 (50.5) | 923 (48.1) | 1063 (50.5) | 1060 (49.9) | 555 (53.5) | — | 732 (59.4) | 960 (49.1) | 944 (46.3) | 1096 (48.8) | 633 (54.3) | — |
| Denmark — no. (%)† | 8346 (49.7) | — | 486 (49.5) | 994 (51.9) | 1042 (49.5) | 1064 (50.1) | 482 (46.5) | — | 501 (40.6) | 997 (50.9) | 1096 (53.7) | 1151 (51.2) | 533 (45.7) | — |
| BMI | 26.2± 4.8 | −1.45 (−1.59 to −1.31) | 24.9± 4.1 | 26.7± 4.3 | 27.2± 4.2 | 27.6± 4.0 | 27.4± 3.9 | 0.59 (0.52 to 0.67) | 23.5± 4.6 | 25.3± 5.5 | 25.6± 5.0 | 26.2± 5.1 | 26.1± 4.7 | 0.62 (0.54 to 0.71) |
| Systolic BP — mm Hg | 128.2± 16.5 | −11.04 (−11.47 to −10.61) | 129.8± 12.1 | 130.4± 12.8 | 131.9± 14.4 | 137.0± 15.8 | 141.9± 16.9 | 3.24 (2.98 to 3.49) | 115.6± 10.3 | 116.9± 12.1 | 120.3± 14.5 | 127.4± 16.3 | 135.6± 18.0 | 5.06 (4.82 to 5.30) |
| Diastolic BP — mm Hg | 79.3± 11.4 | −4.28 (−4.57 to −3.98) | 75.3± 10.2 | 78.9± 11.1 | 81.6± 11.4 | 85.1± 11.2 | 85.1± 10.5 | 2.76 (2.59 to 2.94) | 72.8± 9.2 | 74.9± 10.1 | 76.9± 11.0 | 79.9± 10.9 | 81.3± 10.5 | 2.20 (2.04 to 2.36) |
| LDL cholesterol — mmol/liter | 3.2± 0.9 | −0.14 (−0.17 to −0.12) | 2.8± 0.8 | 3.3± 0.8 | 3.4± 0.8 | 3.4± 0.9 | 3.2± 0.9 | 0.09 (0.07 to 0.10) | 2.8± 0.7 | 2.9± 0.7 | 3.1± 0.8 | 3.4± 0.8 | 3.4± 0.9 | 0.19 (0.18 to 0.20) |
| HDL cholesterol — mmol/liter | 1.5± 0.4 | 0.29 (0.28 to 0.30) | 1.3± 0.3 | 1.3± 0.3 | 1.3± 0.3 | 1.4± 0.3 | 1.4± 0.3 | 0.03 (0.02 to 0.03) | 1.6± 0.3 | 1.6± 0.4 | 1.6± 0.4 | 1.7± 0.4 | 1.8± 0.4 | 0.06 (0.05 to 0.06) |
| Triglycerides (IQR) — mmol/liter | 0.9 (0.7 to 1.4) | −0.13 (−0.14 to −0.12) | 0.9 (0.6 to 1.4) | 1.0 (0.7 to 1.6) | 1.1 (0.8 to 1.7) | 1.1 (0.8 to 1.7) | 1.1 (0.8 to 1.6) | 0.03 (0.02 to 0.03) | 0.7 (0.5 to 1.0) | 0.8 (0.6 to 1.1) | 0.8 (0.6 to 1.1) | 0.9 (0.7 to 1.4) | 1.0 (0.8 to 1.5) | 0.04 (0.04 to 0.05) |
| Lipoprotein(a) (IQR) — nmol/liter | 23.1 (10.0 to 77.9) | 0.08 (0.05 to 0.12) | 18.6 (7.5 to 63.0) | 21.0 (9.0 to 77.0) | 22.3 (9.9 to 74.1) | 23.2 (10.5 to 74.0) | 26.0 (9.8 to 94.0) | 0.06 (0.04 to 0.08) | 20.6 (8.7 to 68.0) | 21.6 (9.0 to 67.5) | 23.3 (10.4 to 73.3) | 28.4 (12.0 to 95.0) | 30.5 (12.7 to 103.2) | 0.10 (0.08 to 0.12) |
| CRP (IQR) — mg/liter | 1.0 (0.4 to 2.0) | 0.03 (0.01 to 0.05) | 1.0 (0.0 to 1.2) | 1.0 (0.4 to 2.0) | 1.0 (0.6 to 2.0) | 1.0 (1.0 to 2.0) | 1.0 (1.0 to 2.0) | 0.05 (0.03 to 0.06) | 1.0 (0.0 to 2.0) | 1.0 (0.4 to 2.0) | 1.0 (0.4 to 2.0) | 1.0 (0.6 to 2.0) | 1.0 (1.0 to 2.0) | 0.03 (0.02 to 0.05) |
| Lipid-lowering therapy — no./total no. (%) | 1708/ 16,611 (10.3) | 0.66 (0.60 to 0.74) | 8/ 967 (0.8) | 54/ 1884 (2.9) | 167/ 1970 (8.5) | 384/ 2122 (18.1) | 346/ 1037 (33.4) | 2.53 (2.36 to 2.73) | 5/ 1233 (0.4) | 32/ 1957 (1.6) | 63/ 2032 (3.1) | 302/ 2244 (13.5) | 347/ 1165 (29.8) | 3.32 (3.04 to 3.65) |
| Antihypertensive therapy — no./total no. (%) | 1893/ 16,611 (11.4) | 0.79 (0.71 to 0.87) | 9/ 967 (0.9) | 44/ 1884 (2.3) | 145/ 1970 (7.4) | 436/ 2122 (20.5) | 363/ 1037 (35.0) | 2.74 (2.55 to 2.96) | 25/ 1233 (2.0) | 50/ 1957 (2.6) | 126/ 2032 (6.2) | 333/ 2244 (14.8) | 362/ 1165 (31.1) | 2.59 (2.40 to 2.79) |
| Antidiabetic therapy — no./total no. (%) | 1169/ 16,611 (7.0) | 1.52 (1.34 to 1.71) | 13/ 967 (1.3) | 62/ 1884 (3.3) | 97/ 1970 (4.9) | 165/ 2122 (7.8) | 115/ 1037 (11.1) | 1.60 (1.47 to 1.74) | 37/ 1233 (3.0) | 156/ 1957 (8.0) | 185/ 2032 (9.1) | 235/ 2244 (10.5) | 104/ 1165 (8.9) | 1.24 (1.16 to 1.32) |
| Obesity — no./total no. (%) | 2989/ 16,798 (17.8) | 0.79 (0.73 to 0.86) | 103/ 982 (10.5) | 339/ 1916 (17.7) | 441/ 2103 (21.0) | 505/ 2124 (23.8) | 207/ 1037 (20.0) | 1.18 (1.13 to 1.24) | 101/ 1231 (8.2) | 324/ 1957 (16.6) | 334/ 2037 (16.4) | 428/ 2246 (19.0) | 207/ 1165 (17.8) | 1.19 (1.13 to 1.24) |
| Family history of CVD — no./total no. (%) | 4073/ 16,567 (24.6) | 1.16 (1.08 to 1.25) | 152/ 947 (16.1) | 411/ 1885 (21.8) | 515/ 2083 (24.7) | 518/ 2113 (24.5) | 272/ 1030 (26.4) | 1.13 (1.08 to 1.18) | 201/ 1183 (17.0) | 473/ 1928 (24.5) | 500/ 2018 (24.8) | 661/ 2227 (29.7) | 370/ 1153 (32.1) | 1.19 (1.15 to 1.24) |
| Smoker — no./total no. (%) | | | | | | | | | | | | | | |
| Current | 1861/ 16,533 (11.3) | 0.92 (0.84 to 1.02) | 127/ 945 (13.4) | 267/ 1884 (14.2) | 243/ 2080 (11.7) | 211/ 2107 (10.0) | 90/ 1030 (8.7) | 0.86 (0.81 to 0.91) | 150/ 1181 (12.7) | 221/ 1918 (11.5) | 209/ 2011 (10.4) | 240/ 2226 (10.8) | 103/ 1151 (8.9) | 0.91 (0.87 to 0.96) |
| Former | 5730/ 16,533 (34.7) | 1.08 (1.01 to 1.15) | 182/ 945 (19.3) | 530/ 1884 (28.1) | 677/ 2080 (32.5) | 814/ 2107 (38.6) | 521/ 1030 (50.6) | 1.39 (1.34 to 1.45) | 233/ 1181 (19.7) | 511/ 1918 (26.6) | 737/ 2011 (36.6) | 940/ 2226 (42.2) | 585/ 1151 (50.8) | 1.44 (1.38 to 1.49) |
| Never | 8942/ 16,533 (54.1) | 0.96 (0.91 to 1.03) | 636/ 945 (67.3) | 1087/ 1884 (57.7) | 1160/ 2080 (55.8) | 1082/ 2107 (51.4) | 419/ 1030 (40.7) | 0.79 (0.77 to 0.82) | 798/ 1181 (67.6) | 1186/ 1918 (61.8) | 1065/ 2011 (53.0) | 1046/ 2226 (47.0) | 463/ 1151 (40.2) | 0.75 (0.72 to 0.77) |



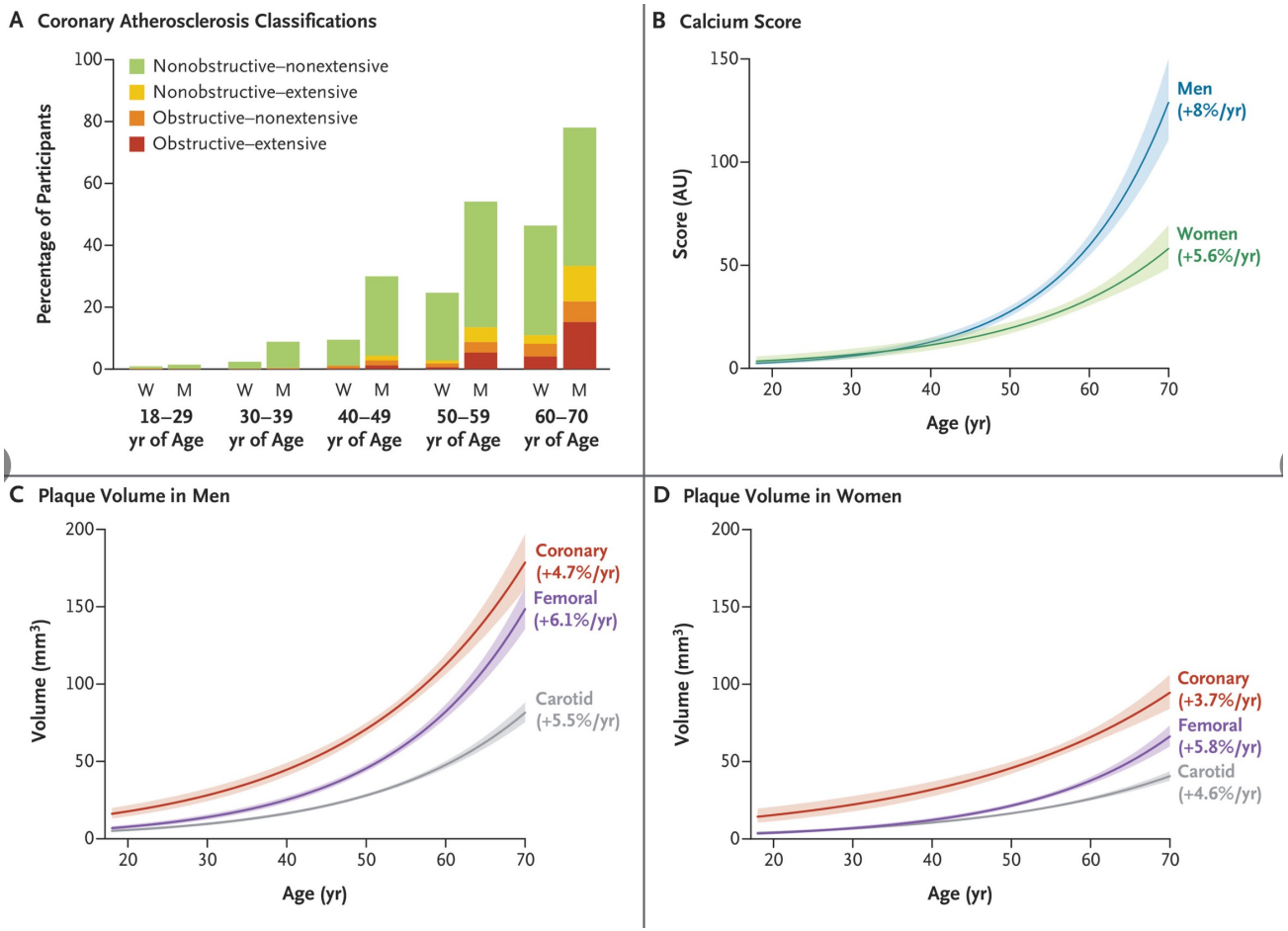

**Prevalence of Peripheral and Coronary-Artery Silent Atherosclerosis throughout Adult Life.**

Panel A shows a cross-sectional age pattern of silent atherosclerosis prevalence in men and women. Panel B shows the distribution of atherosclerosis in the three arterial vascular territories (coronary, femoral, and carotid), stratified according to age and sex. Panel C shows the prevalence of atherosclerosis among male participants in any territory and for each vascular site, and Panel D shows the same data for female participants. For each age stratum, the prevalence and exact Clopper–Pearson 95% confidence intervals are shown. The lines represent logistic-regression models that accounted for age with the use of a natural cubic spline (3 degrees of freedom), and shading in Panels A, C, and D indicate pointwise 95% confidence intervals. I bars indicate exact Clopper–Pearson 95% confidence intervals. The confidence intervals are unadjusted and should be interpreted as descriptive and not used for hypothesis testing.



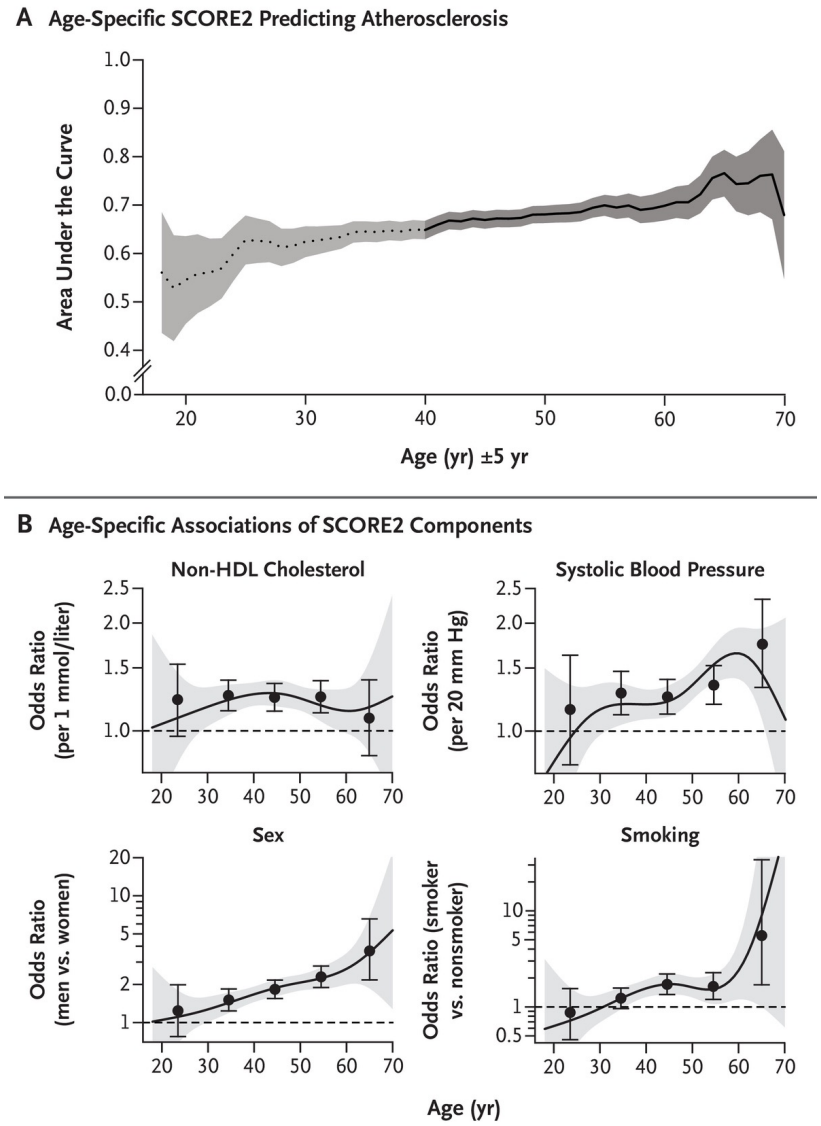

**Age-Related Distribution of Silent Atherosclerosis across Vascular Territories According to Sex.**

Bars show the percentage of participants with plaque in the indicated arterial vascular territories within each age stratum. Percentages were calculated on the basis of all participants of the same sex and age stratum. I bars indicate 95% confidence intervals. The confidence intervals are unadjusted and should be interpreted as descriptive and not used for hypothesis testing.




**Age-Related Differences in Plaque Burden across Vascular Territories.**

Panel A shows the percentage of participants with coronary atherosclerosis that was classified as obstructive (≥50% stenosis in at least one of the 17 coronary segments) or nonobstructive (<50% stenosis in all segments) and as extensive (stenosis in more than 5 of the 17 coronary segments) or nonextensive (stenosis in fewer than 5 segments). Panel B shows the cross-sectional calcium scores (in Agatston units [AU], a measurement of coronary-artery calcification) in participants with calcium scores of greater than 0 for men (coefficient of determination [$R^2$]=11.4%) and women ($R^2$=6.4%). Panels C and D show predicted cross-sectional plaque volume in participants with plaque, with cross-sectional age-related patterns consistent with an exponential increase, for the respective arterial territory. Shading indicates 95% confidence intervals. Panel C shows predicted plaque volumes in men: carotid arteries ($R^2$=17.6%), femoral arteries ($R^2$=17.5%), and coronary arteries ($R^2$=10.7%). Panel D shows predicted plaque volumes in women: carotid arteries ($R^2$=14.4%), femoral arteries ($R^2$=15.0%), and coronary arteries ($R^2$=7.0%).




**Association between Cardiovascular Risk Factors and Silent Atherosclerosis.**

Panel A shows the area under the curve (AUC) for age-specific discrimination in predictions of silent atherosclerosis estimated with the use of the Systematic Coronary Risk Evaluation 2 (SCORE2) framework, which predicts the 10-year risk of fatal and nonfatal cardiovascular disease in European persons 40 to 69 years of age, with higher scores indicating higher risk. For each age, the AUC is calculated for participants within ±5 years (e.g., at age 50 the AUC is calculated for participants 45 to 55 years of age). The line represents the AUC, and the darker shaded area indicates pointwise 95% confidence intervals (DeLong test). The dashed line represents the prediction for participants younger than 40 years of age, and the lighter shading denotes that a SCORE2 is not calibrated for participants younger than 40 years of age. Panel B shows age-specific associations of SCORE2 components with silent atherosclerosis. Curves show adjusted odds ratios for each component as a function of age, estimated from logistic models using a natural cubic spline for age and the component–age interaction. The shaded area represents the pointwise 95% confidence interval. Points are odds ratios within each age stratum, and error bars show the 95% confidence intervals. All the models were adjusted for country and the other SCORE2 components. The confidence intervals are unadjusted and should be interpreted as descriptive and not used for hypothesis testing.

## Discussion

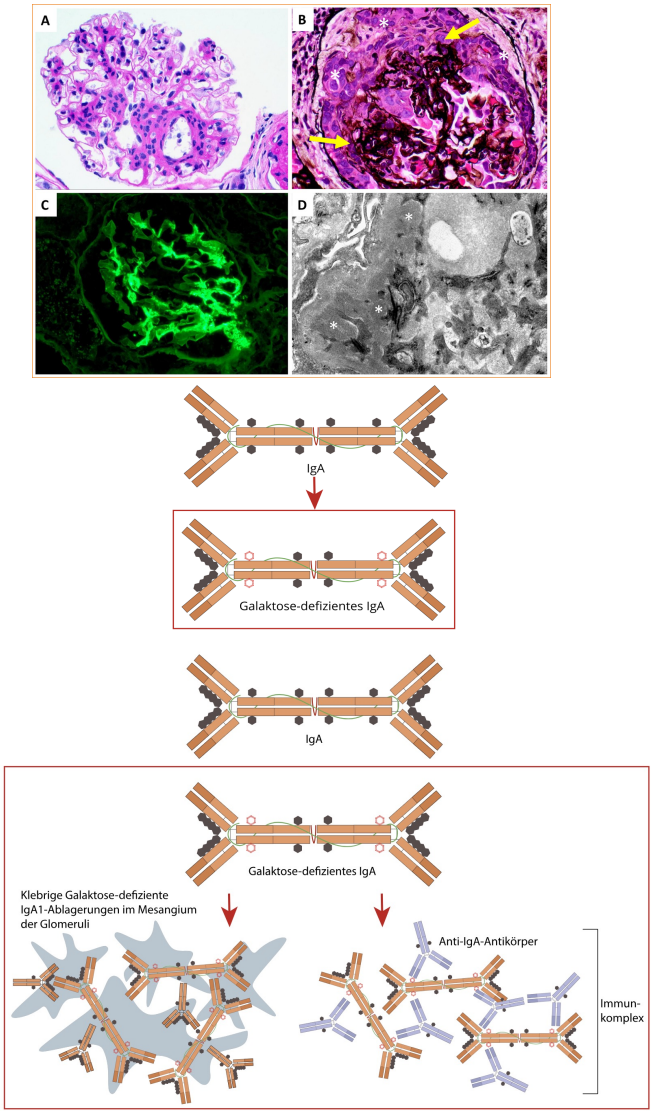
In this large, systematic, cross-sectional, imaging study of adults 18 to 70 years of age without known atherosclerotic cardiovascular disease, silent atherosclerosis was already detectable in approximately 1 in 13 participants who were 18 to 29 years of age, and the prevalence increased sigmoidally to 9 in 10 participants by 60 to 70 years of age. Prevalence increased earlier in men, whereas women showed a later and particularly steep midlife increase. In addition, increasing age was associated with more frequent multiterritorial atherosclerosis and an exponential increase in plaque volume. These data support the concept of silent atherosclerosis as a systemic, progressive disease process in which men had an atherosclerotic phenotype that developed 5 to 10 years earlier than that of women.

This cross-sectional study provides a large-scale atlas of silent atherosclerosis across adult life in men and women. Silent atherosclerosis showed age- and sex-related increases in the cross-sectional prevalence and extent of systemic involvement. Most participants with silent coronary atherosclerosis had peripheral atherosclerosis. Conventional 10-year risk classification identified only a minority of participants with established silent atherosclerosis.

Die **IgA-Nephropathie** (auch *IgA-Nephritis* oder *Morbus Berger*) ist die weltweit häufigste Form einer chronischen Entzündung der Nierenkörperchen (Glomerulonephritis).

**Was passiert im Körper?**

- **Fehlgebildete Antikörper:** Der Körper produziert veränderte Immunglobulin-A1-Moleküle (galaktosedefizientes IgA1).
- **Ablagerung:** Gegen diese Moleküle bilden sich Autoantikörper. Die daraus entstehenden Immunkomplexe lagern sich im Filtergewebe der Niere (Mesangium) ab.
- **Entzündung:** Dies aktiviert das Komplementsystem, was zu einer schleichenden Entzündung, Vernarbung und langfristig zu einem Verlust der Filterfunktion führen kann.

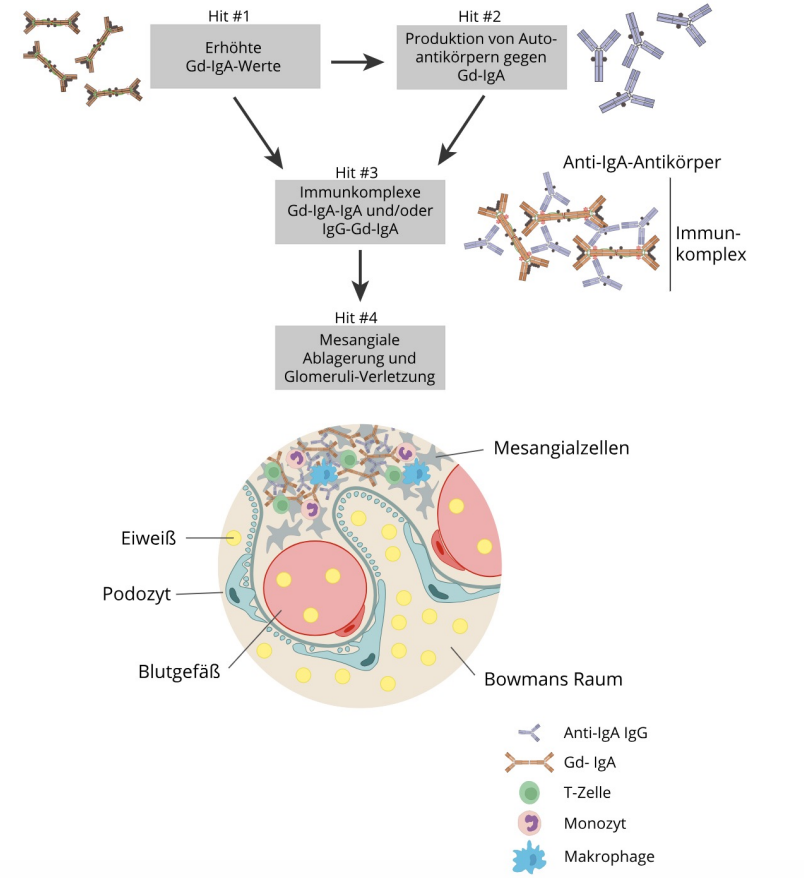


**1. Produktion und Ansammlung von falsch aufgebautem IgA1.** Menschen mit IgAN haben erhöhte IgA-Werte im Blut, das geringere Mengen des speziellen Zuckers Galaktose enthält als normal. Wahrscheinlich sind dafür mehrere Faktoren verantwortlich: genetische Veranlagung, bakterielle Infektionen, Überempfindlichkeit des lymphatischen Gewebes im Darm, in manchen Fällen akute oder chronische entzündliche Darmerkrankungen oder Zöliakie.

**2. Produktion von IgG-Autoantikörpern gegen Gd-IgA1.** Das Vorhandensein von Galaktose-defizientem IgA1 (Gd-IgA1) und dessen Eindringen in den Kreislauf stimuliert die Entwicklung von IgG-Autoantikörpern gegen Gd-IgA1 selbst.

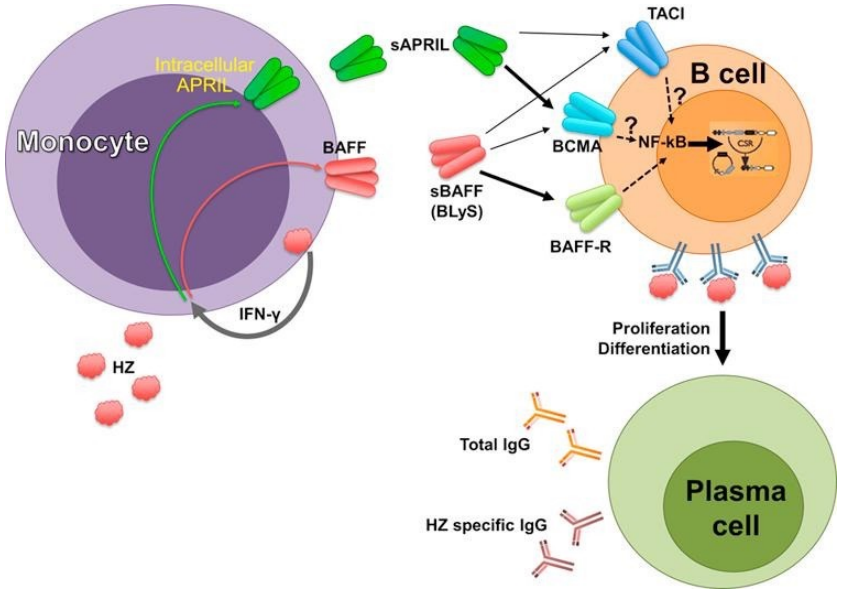
**3. Bildung von Immunkomplexen.** Das Vorhandensein von Immunkomplexen, die aus Galaktose-defizientem IgA selbst und/oder IgA-IgG-Komplexen bestehen, fördert deren Bindung an Rezeptoren und Ablagerung in den Glomeruli/Mesangium.

**4. Ablagerung von Ablagerungen in den Glomeruli.** Aktivierung des Komplementsystems und Entzündungsreaktionen. Degenerative Veränderungen in den Nieren. Die Ablagerungen stimulieren eine Entzündungsreaktion und die Aktivierung des Komplementsystems, gefolgt von der Teilung der Mesangialzellen und einer Überproduktion von Matrix. Die Aktivierung des Komplementsystems kann die Entzündungsreaktion und den Umbau der Struktur des Glomerulums verstärken.

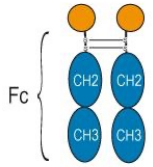


**BAFF** und **APRIL** sind zwei wichtige Signalproteine (Zytokine) aus der Familie des Tumornekrosefaktors (TNF), die eine zentrale Rolle im Immunsystem – insbesondere bei der Reifung, dem Überleben und der Funktion von B-Zellen und Plasmazellen – spielen.

- **BAFF** (*B-cell activating factor*, auch bekannt als *BLyS*):
  - Wirkt als lebenswichtiger Überlebens- und Differenzierungsfaktor für unreife und reife B-Zellen.
  - Bindet an drei verschiedene Rezeptoren: **BAFF-R**, **TACI** und **BCMA**.
- **APRIL** (*A proliferation-inducing ligand*):
  - Teilverwandt mit BAFF; beeinflusst ebenfalls das Überleben und die Klassenwechsel-Rekombination von B-Zellen und ist besonders wichtig für langlebige Plasmazellen (z. B. im Knochenmark).
  - Bindet an die Rezeptoren **TACI** und **BCMA** (teilt sich diese also teilweise mit BAFF).

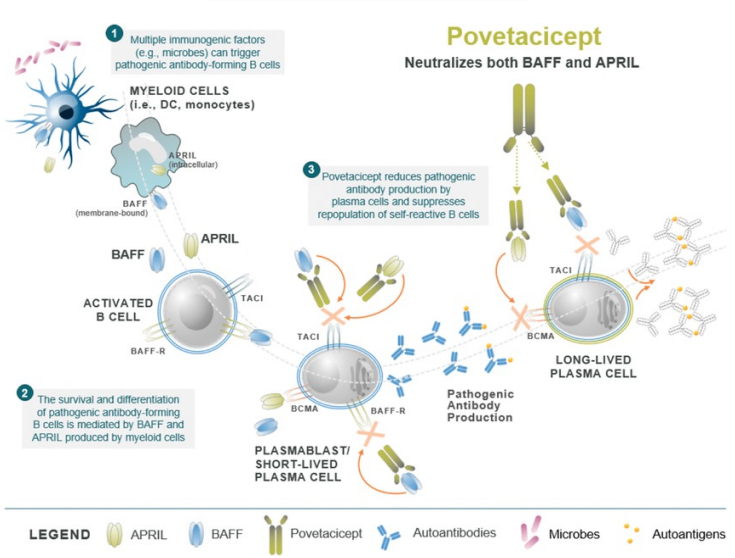


**Povetacicept** ist ein experimenteller, gentechnisch hergestellter Fusionsprotein-Wirkstoff (ein TACI-Fc-Fragment), der von Vertex Pharmaceuticals (nach Übernahme von Alpine Immune Sciences) entwickelt wird.




## Hauptmechanismus

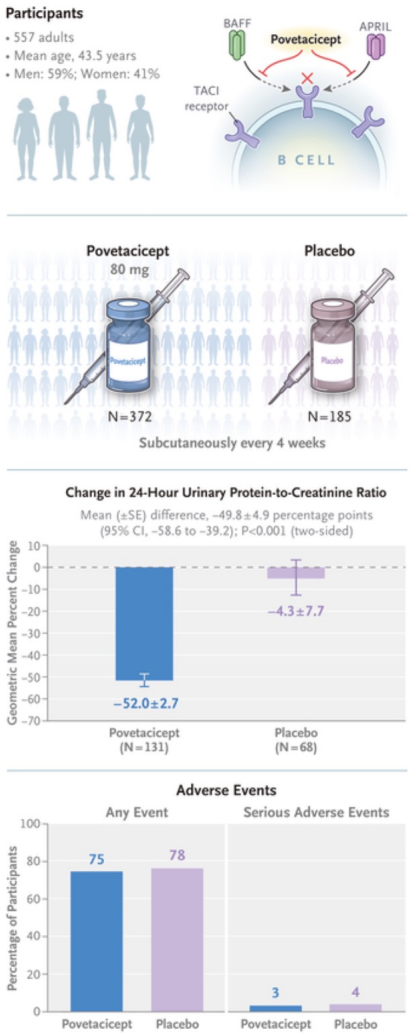
- **Wirkung:** Es ist ein dualer Inhibitor der Zytokine **BAFF** (B-cell activating factor) und **APRIL** (a proliferation-inducing ligand).
- **Ziel:** Durch die Blockade von BAFF und APRIL kontrolliert und reguliert es überaktive B-Zellen und die Bildung von pathogenen Immunkomplexen (wie galaktose-defizitärem IgA1), die bei Autoimmunerkrankungen eine Rolle spielen.



# Interim Analysis of a Phase 3 Trial of Povetacicept in IgA Nephropathy

B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) have distinct roles in IgA-producing B-cell populations and appear to be central to the pathogenesis of IgA nephropathy. Povetacicept, an enhanced, variant transmembrane activator and calcium-modulator and cyclophilin-ligand interactor (TACI)–Fc fragment fusion therapeutic, is engineered for dual inhibition of BAFF and APRIL.

In this ongoing, phase 3, double-blind, placebo-controlled trial, participants with biopsy-proven IgA nephropathy receiving stable background therapy were randomly assigned in a 2:1 ratio to receive povetacicept at a dose of 80 mg or placebo subcutaneously every 4 weeks. The primary end point of this prespecified interim analysis was the change in the 24-hour urinary protein-to-creatinine ratio at week 36. Secondary end points were the change at week 36 in galactose-deficient IgA1 levels and hematuria resolution at week 36 among participants with baseline hematuria.



Povetacicept was engineered with a TACI domain that confers a greater binding affinity to BAFF and APRIL than wild-type TACI, with evidence of increased potency, improved pharmacokinetics, and broader tissue distribution.

In a phase 1–2, open-label study (RUBY-3), povetacicept at a dose of 80 mg every 4 weeks led to sustained reductions in disease-activity measures among 21 adults with IgA nephropathy receiving stable background therapy — 24-hour urinary protein-to-creatinine ratio at week 48 was reduced by 64%, along with reductions in galactose-deficient IgA1 levels, resolution of hematuria, and stabilization of eGFR. In the phase 3 RAINIER AIS-D08 trial, we evaluated the efficacy and safety of povetacicept in adults with biopsy-confirmed IgA nephropathy at risk for disease progression and receiving stable background therapy. Here we report the prespecified interim analysis of this multicenter trial.

**Trial Design and Participants**

Our trial is an ongoing, phase 3, double-blind, randomized, placebo-controlled, 2-year trial of the efficacy and safety of povetacicept in participants with IgA nephropathy receiving medication to lower proteinuria as stable background therapy (with proteinuria assessed as the 24-hour urinary protein-to-creatinine ratio).

Participants were randomly assigned in a 2:1 ratio to receive povetacicept at a dose of 80 mg or placebo subcutaneously every 4 weeks through week 100. Randomization was stratified according to 24-hour urinary protein-to-creatinine ratio (≤1.5 vs. >1.5, with protein and creatinine both measured in grams), as a measure of proteinuria; eGFR (30 to <60 vs. ≥60 ml per minute per 1.73 $m^2$); and geographic region (Japan vs. other Asia–Pacific vs. the rest of the world).
Adults with biopsy-proven IgA nephropathy, 24-hour urinary protein excretion of at least 1 g per day or 24-hour urinary protein-to-creatinine ratio of at least 0.75, and an eGFR of at least 30 ml per min per 1.73 $m^2$ were eligible. Participants were required to have received a stable and maximum tolerated dose of angiotensin-converting enzyme inhibitor or angiotensin II–receptor blocker for at least 12 weeks before screening. Use of other medications that lower proteinuria (e.g., an SGLT2 inhibitor) was allowed.

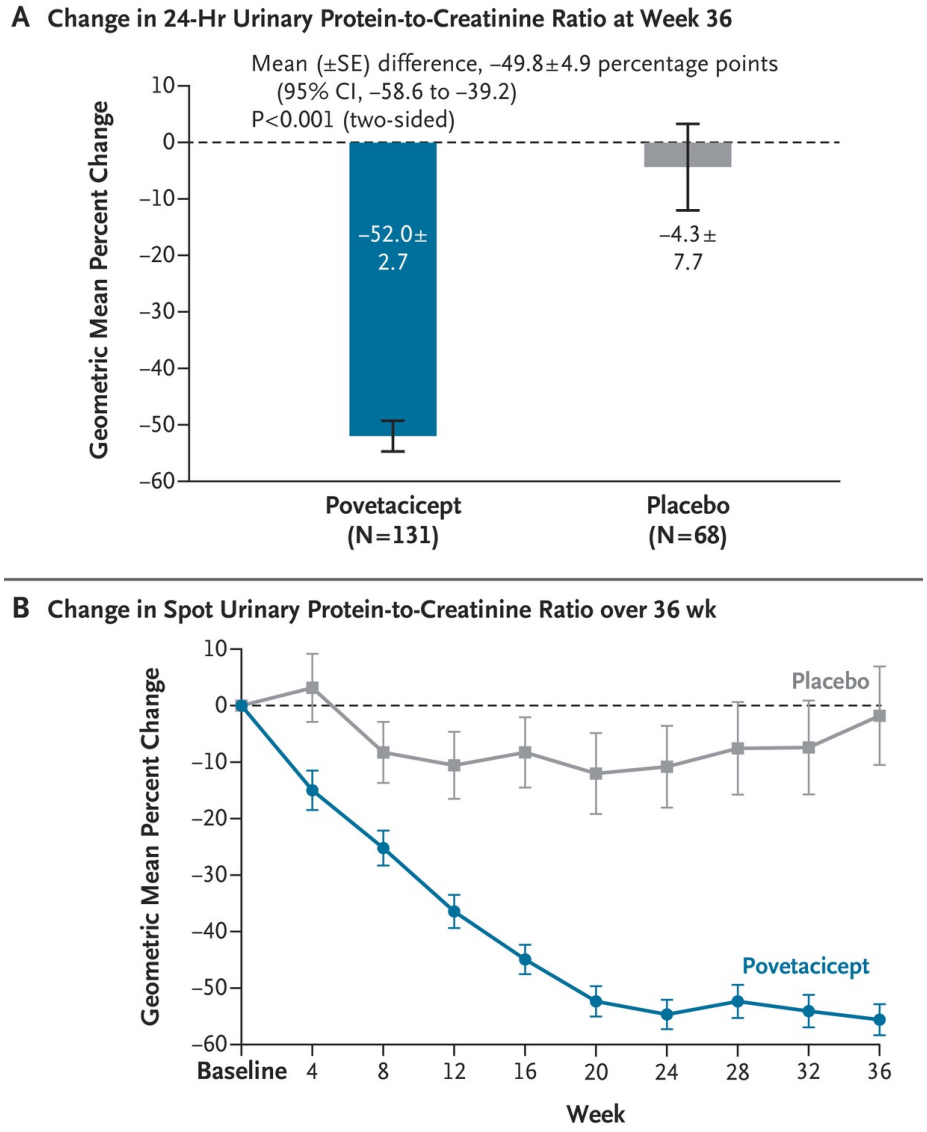
**End Points**

The primary end point for this interim analysis was the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36. The secondary end points for the interim analysis were the change in galactose-deficient IgA1 levels from baseline to week 36 and resolution of hematuria at week 36.

| Characteristic | Povetacicept (N=131) | Placebo (N=68) |
|---|---|---|
| Age — yr | 44.1±12.5 | 42.5±11.8 |
| Sex — no. (%) | | |
| Male | 76 (58) | 42 (62) |
| Female | 55 (42) | 26 (38) |
| Race — no. (%)† | | |
| Asian | 82 (63) | 40 (59) |
| White | 47 (36) | 26 (38) |
| Other | 2 (2) | 2 (3) |
| Geographic region — no. (%)‡ | | |
| Asia–Pacific | 76 (58) | 41 (60) |
| Europe and the Middle East | 31 (24) | 17 (25) |
| North America | 24 (18) | 10 (15) |
| Time from initial renal biopsy to randomization — yr | 4.2±4.2 | 4.9±4.4 |
| 24-hour urinary protein-to-creatinine ratio§ | | |
| Mean | 1.5±0.9 | 1.6±1.4 |
| Distribution — no. (%) | | |
| ≤1.5 | 82 (63) | 43 (63) |
| >1.5 | 49 (37) | 25 (37) |
| eGFR§ | | |
| Mean — ml/min/1.73 $m^2$ | 74.4±30.3 | 68.4±29.5 |
| Distribution — no. (%) | | |
| <60 ml/min/1.73 $m^2$ | 54 (41) | 30 (44) |
| ≥60 ml/min/1.73 $m^2$ | 77 (59) | 38 (56) |
| Galactose-deficient IgA1 — ng/ml | 6591.7±4682.1 | 6169.7±4589.0 |
| Hematuria — no. (%) | | |
| None | 31 (24) | 15 (22) |
| Low | 33 (25) | 17 (25) |
| Moderate | 42 (32) | 20 (29) |
| High | 25 (19) | 16 (24) |
| Blood pressure — mm Hg§ | | |
| Systolic | 122.8±12.9 | 123.9±11.4 |
| Diastolic | 77.9±8.9 | 80.4±7.4 |
| Previous immunosuppression for IgA nephropathy — no. (%)¶ | 17 (13) | 10 (15) |
| Medications that lower proteinuria — no. (%)‖ | | |
| Any | 130 (99) | 68 (100) |
| ACE inhibitor or ARB | 127 (97) | 67 (99) |
| SGLT2 inhibitor | 88 (67) | 43 (63) |
| Mineralocorticoid receptor antagonist | 19 (15) | 8 (12) |
| Any Endothelin A receptor antagonist | 2 (2) | 2 (3) |

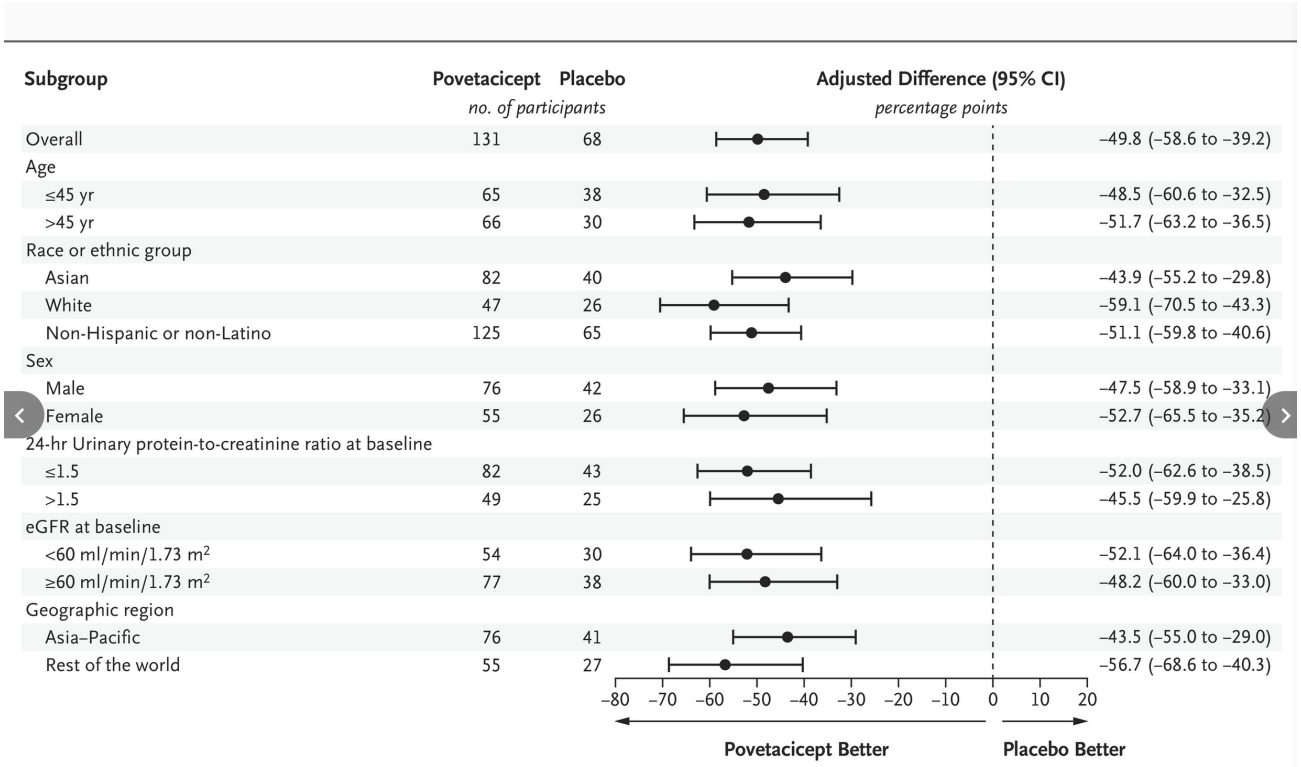
# Adverse Events

| Event | Povetacicept (N=372) | Placebo (N=185) |
|---|---|---|
| | *number of participants (percent)* | |
| Any adverse event | 279 (75) | 145 (78) |
| Mild | 153 (41) | 84 (45) |
| Moderate | 115 (31) | 53 (29) |
| Severe | 11 (3) | 8 (4) |
| Infection† | 171 (46) | 75 (41) |
| Mild | 105 (28) | 43 (23) |
| Moderate | 64 (17) | 31 (17) |
| Severe | 2 (1) | 1 (1) |
| Any adverse event considered to be related to trial regimen‡ | 117 (31) | 37 (20) |
| Events occurring in ≥10% of participants in either trial group | | |
| Upper respiratory tract infection | 68 (18) | 21 (11) |
| Nasopharyngitis | 36 (10) | 23 (12) |
| Injection-site reaction§ | 54 (15) | 4 (2) |
| Any serious adverse event | 11 (3) | 8 (4) |
| Infection | 2 (1) | 1 (1) |
| Any adverse event leading to discontinuation of trial regimen¶ | 1 (<1) | 4 (2) |
| Any adverse event leading to death | 0 | 0 |



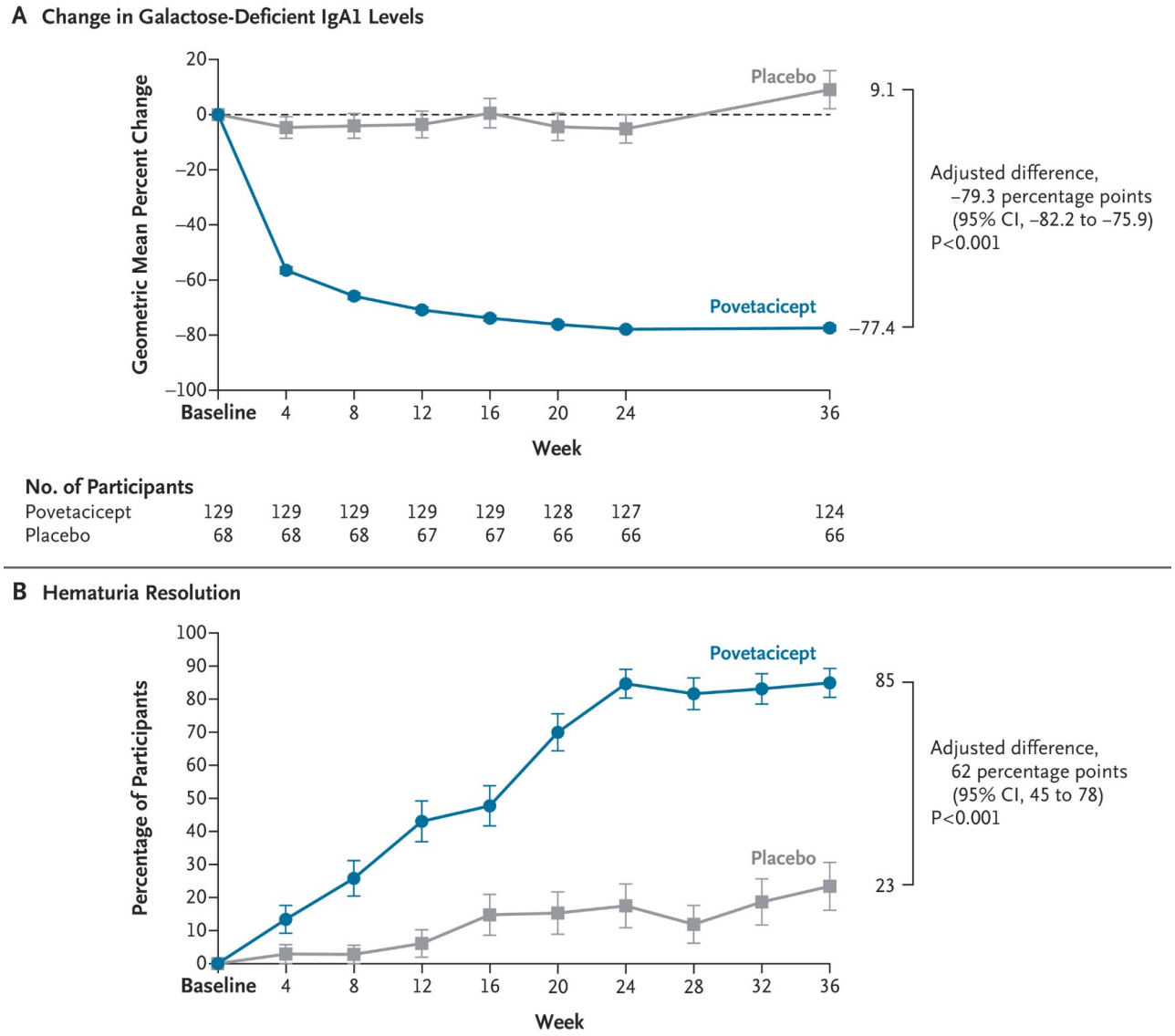

**Percent Change in 24-Hour Urinary Protein-to-Creatinine Ratio (Primary End Point) and in Spot Urinary Protein-to-Creatinine Ratio.**

Panel A shows the geometric mean percent change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36 (multiplicity-controlled primary end point) in the primary analysis population for the interim analysis. Panel B shows the geometric mean percent change in the spot urinary protein-to-creatinine ratio (an exploratory end point) from baseline to 36 weeks in the primary analysis population for the interim analysis. The primary analysis population for the interim analysis comprised the first 199 participants who had undergone randomization and either had completed the week 36 visit or had discontinued the trial regimen early and had received the first dose at least 36 weeks before the data-cutoff date for the interim analysis. For the 24-hour urinary protein-to-creatinine ratio, both protein and creatinine were measured in grams. I bars indicate the standard error. A mixed-effects model for repeated measures was used to analyze the percent change in the 24-hour and spot urinary protein-to-creatinine ratio relative to baseline. The mixed-effects model for repeated measures included data assessed on a natural log scale up to week 36, with region (Asia–Pacific vs. the rest of the world), trial group, visit, and trial group–by–visit interaction as fixed effects and baseline estimated glomerular filtration rate and baseline urinary protein-to-creatinine ratio (assessed on a natural log scale) as covariates. Results from the model were back-transformed from a log scale, with percent change from baseline calculated as the estimated geometric mean ratio minus 1, times 100%.



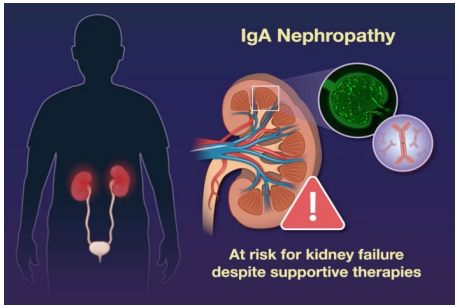

**Prespecified Subgroup Analyses of the Primary End Point.**

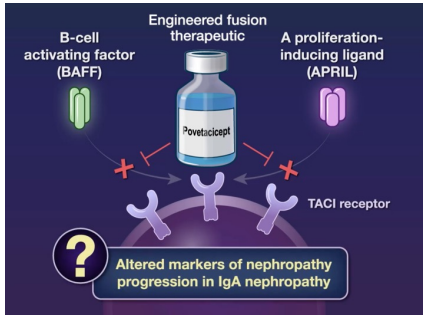
Shown is a forest plot for the prespecified subgroup analyses of the change in the 24-hour urinary protein-to-creatinine ratio from baseline to week 36 (the primary end point). The percent change is based on the adjusted difference between povetacicept and placebo. Race and ethnic group were reported by the participants. For the 24-hour urinary protein-to-creatinine ratio, both protein and creatinine were measured in grams. Confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The abbreviation eGFR denotes estimated glomerular filtration rate.

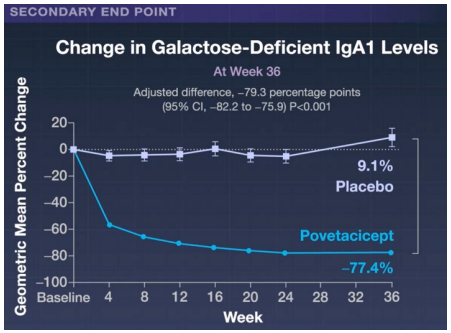


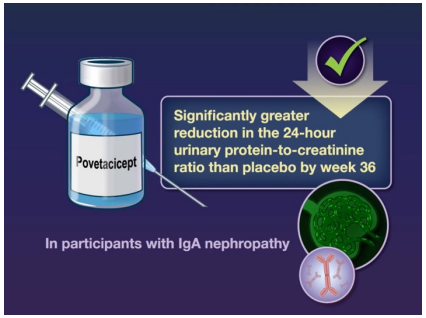

**Percent Change in Galactose-Deficient IgA1 Levels and Resolution of Hematuria.**

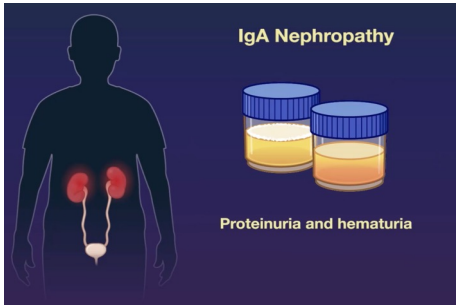
Panel A shows the geometric mean percent change in serum galactose-deficient IgA1 levels at week 36 (multiplicity-controlled secondary end point) and the change over time through week 36. Panel B shows the percentage of participants who had hematuria resolution at week 36 (multiplicity-controlled secondary end point) and the change over time through week 36. Hematuria at baseline was defined as moderate or large amounts of blood in the urine according to a dipstick test. Hematuria resolution was defined as a decrease to no or low levels of blood in the urine of the participants with hematuria at baseline. I bars indicate the standard error.

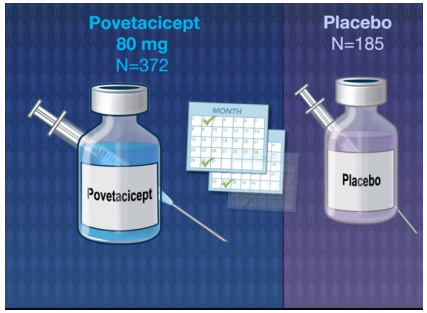

IgA Nephropathy
At risk for kidney failure
despite supportive therapies

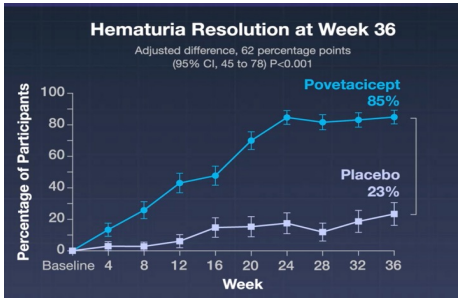

B-cell
activating factor
(BAFF)
Engineered fusion
therapeutic
A proliferation-
inducing ligand
(APRIL)
Povetacicept
TACI receptor
Altered markers of nephropathy
progression in IgA nephropathy

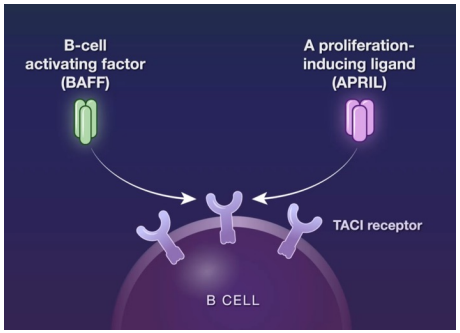

SECONDARY END POINT
Change in Galactose-Deficient IgA1 Levels
At Week 36
Adjusted difference, −79.3 percentage points
(95% CI, −82.2 to −75.9) P<0.001
Geometric Mean Percent Change
9.1%
Placebo
Povetacicept
−77.4%
Week

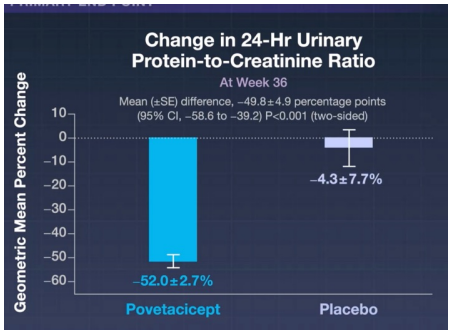

Povetacicept
Significantly greater
reduction in the 24-hour
urinary protein-to-creatinine
ratio than placebo by week 36
In participants with IgA nephropathy

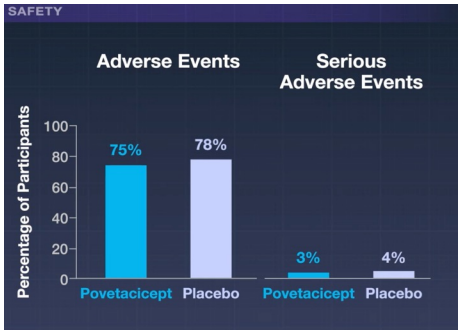

IgA Nephropathy
Proteinuria and hematuria


Povetacicept
80 mg
N=372
Placebo
N=185
Povetacicept
Placebo


Hematuria Resolution at Week 36
Adjusted difference, 62 percentage points
(95% CI, 45 to 78) P<0.001
Percentage of Participants
Povetacicept
85%
Placebo
23%
Week


B-cell
activating factor
(BAFF)
A proliferation-
inducing ligand
(APRIL)
TACI receptor
B CELL


Change in 24-Hr Urinary
Protein-to-Creatinine Ratio
At Week 36
Mean (±SE) difference, −49.8±4.9 percentage points
(95% CI, −58.6 to −39.2) P<0.001 (two-sided)
Geometric Mean Percent Change
−4.3±7.7%
−52.0±2.7%
Povetacicept
Placebo


SAFETY
Adverse Events
Serious
Adverse Events
Percentage of Participants
75%
78%
3%
4%
Povetacicept
Placebo
Povetacicept
Placebo

Die **Thrombolyse** (Lysetherapie) ist eine medikamentöse Akutbehandlung bei einem ischämischen Schlaganfall (durch ein Blutgerinnsel verursacht). Ziel ist es, das verstopfende Gerinnsel aufzulösen und die Blutversorgung des Gehirns so schnell wie möglich wiederherzustellen.



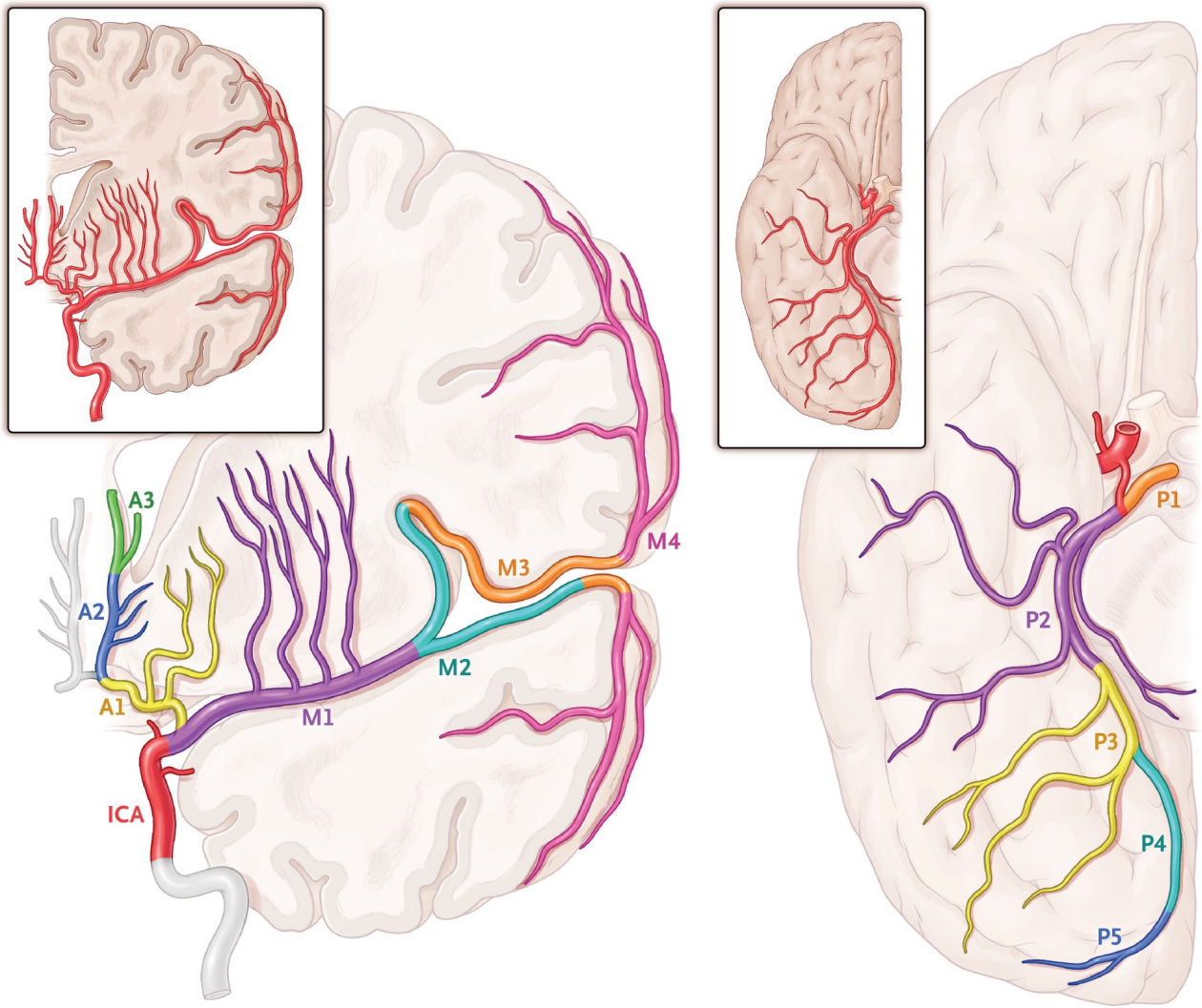
**Das wichtigste Zeitfenster**

- **Klassisch:** Die intravenöse Thrombolyse sollte idealerweise **innerhalb von 4,5 Stunden** nach den ersten Symptomen beginnen.
- **Erweitert:** In speziellen Fällen (nach gezielter Bildgebung via MRT oder Perfusions-CT zum Nachweis von rettbarem Gewebe) kann das Zeitfenster auf **bis zu 9 Stunden** oder bei unklarem Zeitpunkt (z. B. nach dem Aufwachen) ausgedehnt werden.
- **Goldene Regel:** Je früher die Behandlung startet, desto besser sind die Heilungschancen („Time is brain“ / jede Minute zählt).

# Intravenous Thrombolysis for Acute Ischemic Stroke — New Directions

**Summary**

In the past 5 years, substantial changes have been made in the use of intravenous thrombolysis (IVT) in patients with acute ischemic stroke. Integrating IVT with endovascular thrombectomy, which improves outcomes in patients with stroke due to large cerebral vessel occlusion, has been a particular challenge. This review discusses the underlying vascular targets for IVT and thrombectomy, the increasing use of tenecteplase instead of alteplase, broadening indications for the use of IVT, and ancillary drugs and dosing methods that may augment the success of IVT.




**Cerebral Circulation.**

Large-vessel occlusions occur in the internal carotid artery (ICA) and first segment of the middle cerebral artery (M1) and include the vertebral and basilar arteries, which are not shown; these occlusions collectively represent approximately 30% of acute ischemic strokes and are generally treated with endovascular thrombectomy (EVT) with or without intravenous thrombolysis (IVT). Medium-size vessel occlusions are the M2 and M3 branches of the middle cerebral artery, and the proximal anterior cerebral artery (A1) and its first branch (A2), the proximal posterior cerebral artery (P1) and its first branch (P2), which together represent approximately 20% of acute ischemic strokes and are generally treated with IVT and, in some M2 occlusions, with EVT. Distal-vessel occlusions represent the remaining arterial cerebrovascular occlusions, including penetrating vessels, arterioles, and microcirculation; these occlusions represent approximately 50% of acute ischemic strokes and are generally treated with IVT if the stroke is disabling.

KEY POINTS

## Intravenous Thrombolysis for Acute Ischemic Stroke — New Directions

- Intravenous thrombolysis remains the most common reperfusion therapy for patients with acute ischemic stroke.
- Intravenous thrombolysis and endovascular thrombectomy have complementary vascular targets, and appropriate treatment should consider both options.
- Updated published guidelines provide new evidence-based recommendations pertaining to intravenous thrombolysis administration for treating patients who have had minor strokes, who are receiving endovascular thrombectomy, who present more than 4.5 hours after symptom onset, or who are receiving direct-acting anticoagulant therapy.
- Tenecteplase is replacing the tissue plasminogen activator alteplase because of its convenience and equivalent benefit and safety.
- Newer fibrinolytic drugs and alternate dosing strategies may yield improved outcomes.

**Recommended Doses of Tenecteplase for Persons with Acute Ischemic Stroke.**

| Body Weight | Tenecteplase Dose | |
|---|---|---|
| | *mg* | *ml* |
| <60 kg | 15.0 | 3.0 |
| 60 to <70 kg | 17.5 | 3.5 |
| 70 to <80 kg | 20.0 | 4.0 |
| 80 to <90 kg | 22.5 | 4.5 |
| ≥90 kg | 25.0 | 5.0 |

## IVT Combined with Antithrombotic or Antiplatelet Agents

One logical approach to prevent reocclusion of vessels after successful thrombolysis and to augment distal reperfusion has been to couple IVT with antithrombotic or antiplatelet therapies. In general, adding antiplatelet agents or anticoagulants to IVT has resulted in increased risk without benefit.

**Stroke Severity**

The benefit versus risk of IVT in patients who have had mild strokes remains an area of uncertainty. Stroke severity has been measured in two ways. First, a mild stroke has been defined as a neurologic deficit that would not be disabling if it persisted; in such cases, guidelines recommend against IVT. However, the extent of deficit that would be disabling for an individual patient is subjective and varies on the basis of age, activity level, and personal preference.

**Treatment with IVT beyond 3 Hours**

Although treatment administered earlier rather than later has resulted in better outcomes with IVT, the time window of 3 hours that was derived from early trials of IVT has expanded to as long as 24 hours in special circumstances.

**Use of Direct Oral Anticoagulant (DOAC) Therapy**

A common reason for withholding IVT is concurrent use of a DOAC, because these agents are used for stroke prevention in persons with atrial fibrillation, a major risk factor for acute ischemic stroke. DOAC use was previously considered to be an absolute contraindication to IVT because of a potentially increased risk of bleeding, but recent guidelines regard DOAC use within 48 hours before acute ischemic stroke as only a relative contraindication to IVT.

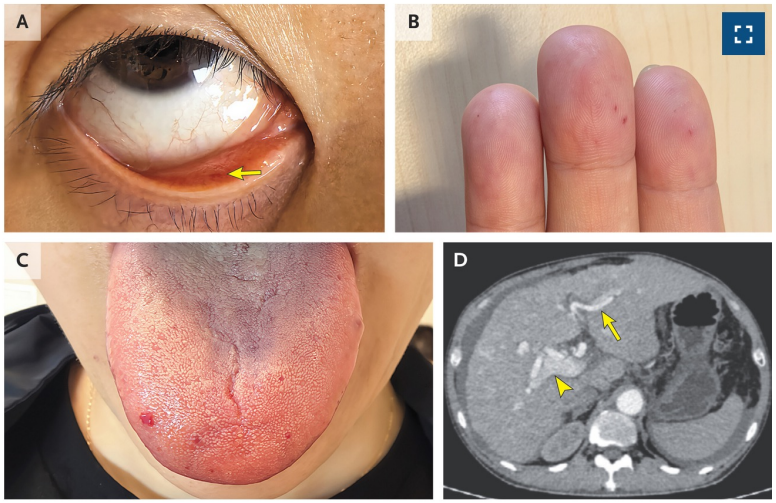
**Coordinating the Use of IVT and EVT**

Trials have shown a significant but modest overall benefit in rates of functional independence with bridging IVT when the duration between IVT and EVT is brief (median, 16 minutes) and there is little time for the thrombolytic agent to act on the clot.

**Conclusion and Future Prospects**

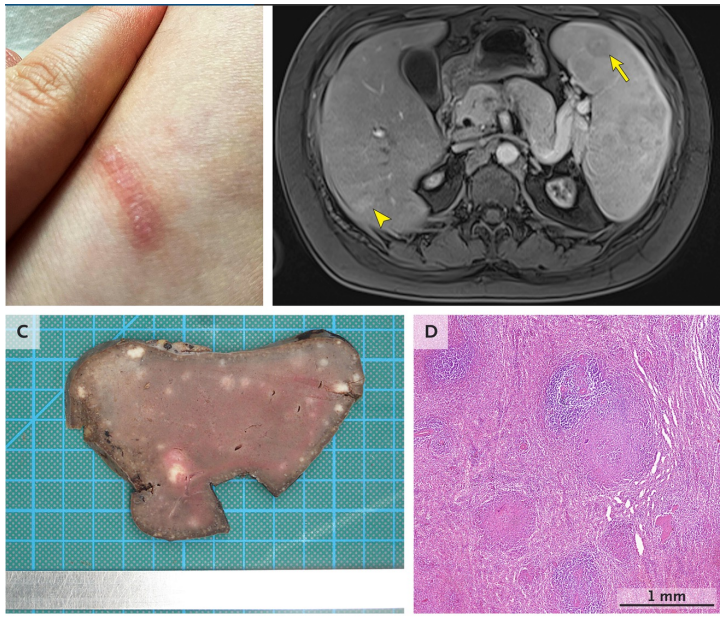
The approaches to the use of IVT, the most common treatment for acute ischemic stroke, have evolved and will continue to do so. More patients will probably receive IVT owing to easing of existing exclusions, expanded availability of imaging and treatment up to (and possibly beyond) 24 hours after onset of symptoms if there is salvageable tissue, enhanced prehospital diagnosis and treatment, and extension of resources to remote or underdeveloped regions. IVT outcomes may be improved by resolving persistent arterial occlusion and impaired microcirculatory flow by the addition of new fibrinolytic agents and multiple dosing strategies.

# Hereditary Hemorrhagic Telangiectasia




A 56-year-old woman was referred to the hepatobiliary surgery clinic for abnormal liver imaging results. She reported 2 months of fatigue and decades of intermittent epistaxis that had recently increased in frequency. Physical examination was notable for telangiectasias on the palpebral conjunctiva (Panel A, arrow), fingertips (Panel B), and tongue (Panel C). Laboratory testing showed a hemoglobin level of 8.9 g per deciliter (reference range, 11.0 to 15.0) and normal results for liver function. Computed tomography of the abdomen with the administration of contrast material showed an enlarged, tortuous hepatic artery (Panel D, arrow) and early opacification of the portal vein (Panel D, arrowhead) and hepatic veins during the arterial phase — findings suggestive of intrahepatic arterioportal and arteriovenous shunting. There was also evidence of portal hypertension. On the basis of the findings of mucocutaneous telangiectasias and hepatic vascular malformations in a patient with recurrent epistaxis, a diagnosis of hereditary hemorrhagic telangiectasia (HHT) was made. Genetic testing identified a pathogenic variant in *ACVRL1*, which is more commonly associated with hepatic vascular malformations in HHT than pathogenic variants in *ENG*, which are more commonly associated with pulmonary and cerebral arteriovenous malformations. Treatment with carvedilol for portal hypertension and thalidomide for antiangiogenesis was initiated. At 6-month follow-up, the epistaxis, anemia, and fatigue had abated.

# Disseminated Bartonellosis




A 29-year-old woman was transferred to a tertiary care hospital for evaluation of fever that had persisted despite extensive testing and empirical treatment. The patient had undergone kidney transplantation 5 years earlier and had been taking tacrolimus, methylprednisolone, and mycophenolic acid. On physical examination, a healing scratch from the patient's cat was noted on the medial right thigh (Panel A). T1-weighted magnetic resonance imaging of the abdomen (Panel B) showed splenomegaly and lesions on the liver (arrowhead) and spleen (arrow). Serum testing for *Bartonella henselae* infection revealed an IgM titer of 1:192 (reference value, <1:12) and an IgG titer of less than 1:64 (reference value, <1:64); a polymerase-chain-reaction (PCR) assay of the serum for *B. henselae* was negative. Treatment with azithromycin and rifampin for possible bartonellosis was initiated. To rule out lymphoma, a splenic biopsy was performed and resulted in hemorrhage that led to splenectomy. Gross examination of the spleen showed whitish nodules (Panel C). Histopathological analysis of splenic tissue showed necrotizing granulomas (Panel D, hematoxylin and eosin stain). A PCR assay of the tissue for *B. henselae* was positive. A diagnosis of disseminated bartonellosis — which can manifest with hepatosplenic involvement in patients with immunodeficiency — was made. Six weeks after finishing treatment, the patient had returned to her usual state of health.

Interactive case from last week

CLINICAL PROBLEM-SOLVING

# An Element Out of Place

A 55-year-old woman with hypertension, type 2 diabetes, fibromyalgia, and psoriatic arthritis presented to the emergency department with a 10-day history of nausea, lightheadedness, and abdominal pain, starting 1 day after she had returned from a 3-week trip to Puerto Rico. Two days before her presentation, slurred speech, unsteady gait, and confusion had developed. During the preceding week, she had also had generalized weakness, constipation, polyuria, polydipsia, and palpitations. She reported chronic pain in both knees. She reported no fevers, chills, cough, chest pain, shortness of breath, dysuria, diarrhea, or rash.

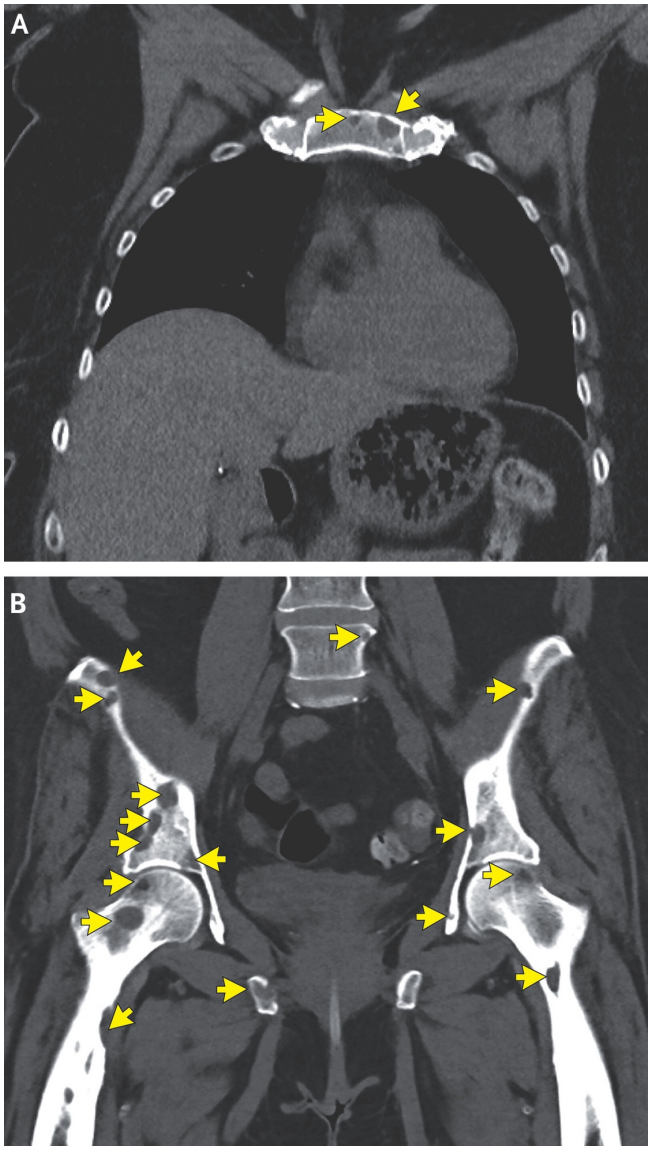
Her previous surgeries included below-the-knee amputation of the right leg for infected nonhealing diabetic ulcers 8 months earlier, as well as cholecystectomy and total laparoscopic hysterectomy with bilateral salpingo-oophorectomy more than 10 years earlier. Her family history included diabetes in maternal and paternal relatives and breast cancer in two paternal aunts. Her medications included ixekizumab (an interleukin-17A inhibitor) for psoriatic arthritis, duloxetine, gabapentin, empagliflozin, and insulin degludec.

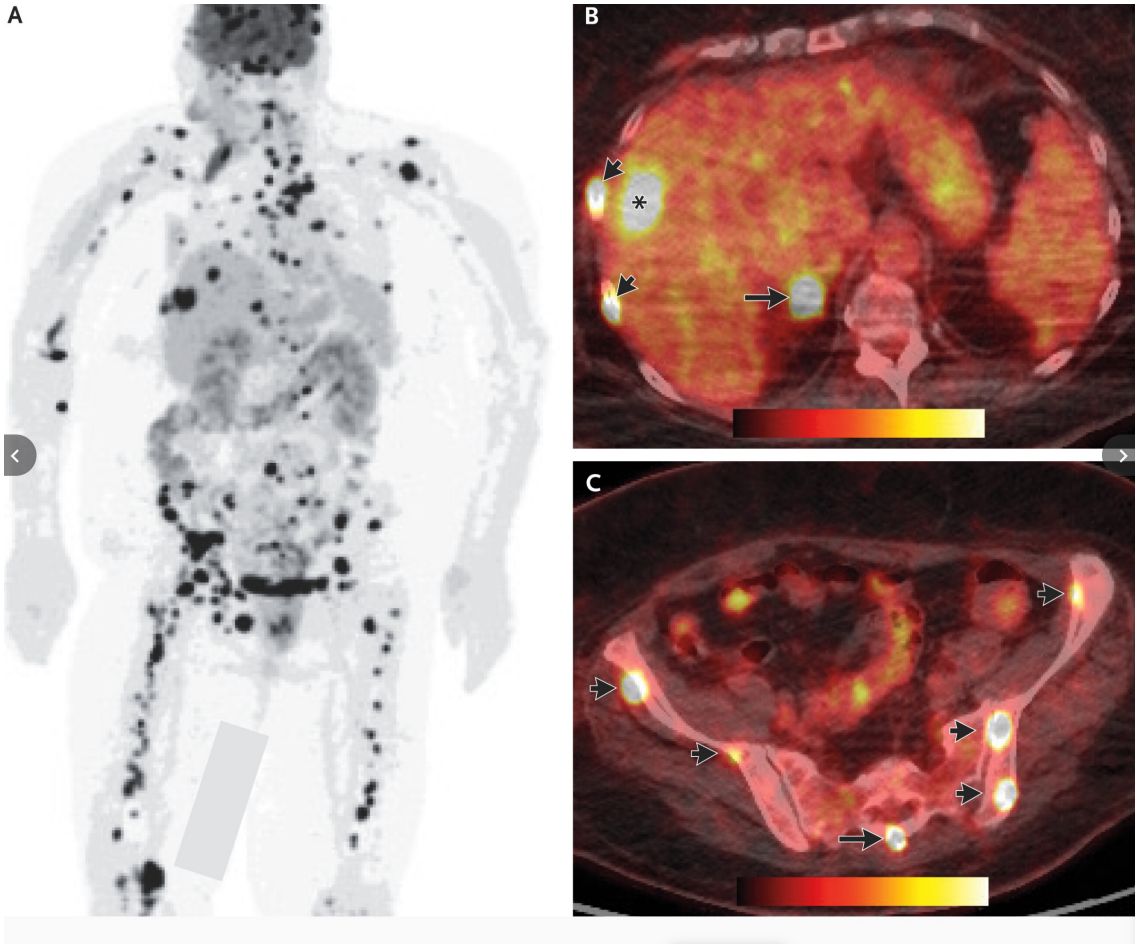
The patient was afebrile. Her blood pressure was 178/81 mm Hg, heart rate 90 beats per minute, and oxygen saturation 99% while she was breathing ambient air. She appeared to be well-nourished. Mucous membranes were dry. No scleral icterus was observed. Cervical lymphadenopathy was absent, and the thyroid examination was normal. Cardiopulmonary and abdominal examinations were normal. The right lower-leg stump was well-healed and nontender; peripheral edema was absent. She had chin and neck hirsutism, mild scalp alopecia, and no rashes, jaundice, or subcutaneous masses. She was somnolent but opened her eyes when spoken to. Despite inattention, she was oriented to self, place, and time. She had no focal neurologic deficits, asterixis, or tremor. Her most recent mammogram (1 year earlier) and colonoscopy (11 years earlier) had been normal. The sodium level was 135 mmol per liter, chloride level 95 mmol per liter, and creatinine level 3.94 mg per deciliter (350 µmol per liter; estimated glomerular filtration rate [eGFR], 13 ml per minute per 1.73 $m^2$ of body-surface area), blood urea nitrogen level 75 mg per deciliter (27.0 mmol per liter), and glucose level 173 mg per deciliter (9.6 mmol per liter). Potassium, bicarbonate, and magnesium levels were normal. The calcium level was 18.9 mg per deciliter (4.72 mmol per liter; normal range, 8.8 to 10.7 mg per deciliter [2.20 to 2.68 mmol per liter]), and the phosphorus level was 5.1 mg per deciliter (1.65 mmol per liter; normal range, 2.4 to 4.3 mg per deciliter [0.80 to 1.40 mmol per liter]).

These laboratory values, including a previous creatinine level (0.92 mg per deciliter [80 µmol per liter]), had been normal 6 weeks earlier. The lactate dehydrogenase level was normal. Liver-enzyme and liver-function tests were normal except for an alkaline phosphatase level of 152 U per liter (normal range, 35 to 130). The glycated hemoglobin level was 7.0%. The hematocrit was 31% (which was similar to the previous value); the white-cell count, differential, and platelet count were normal. The mean corpuscular volume and hemoglobin and mean corpuscular hemoglobin concentrations were uninterpretable owing to red-cell agglutination. The lactate level was normal. Chest radiography did not show pulmonary or bony abnormalities. Renal ultrasonography was unremarkable. The patient received 2 liters of lactated Ringer's solution.

The ionized calcium level was 9.1 mg per deciliter (2.28 mmol per liter; normal range, 4.5 to 5.3 mg per deciliter [1.12 to 1.32 mmol per liter]). The PTH level was 9 pg per milliliter (normal range, 15 to 65).

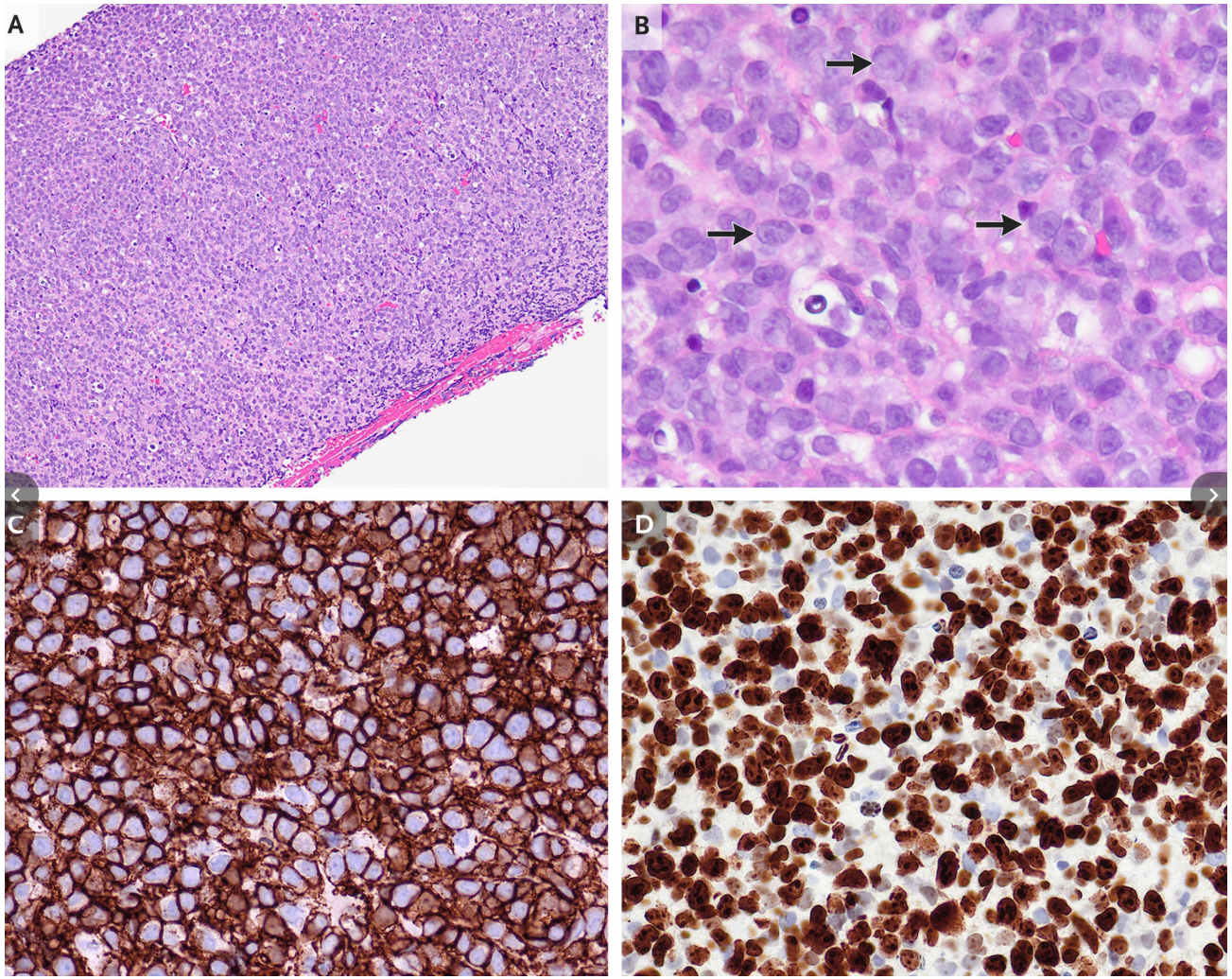
The 1,25 dihydroxyvitamin D and 25-hydroxyvitamin D levels were below detection in each assay: 8 pg per milliliter (normal range, 18 to 78) and 9 ng per milliliter (20 nmol per liter; normal range, 20 to 50 ng per milliliter [50 to 125 nmol per liter]), respectively. Thyrotropin and morning cortisol levels were normal.


A
B


A
B
C

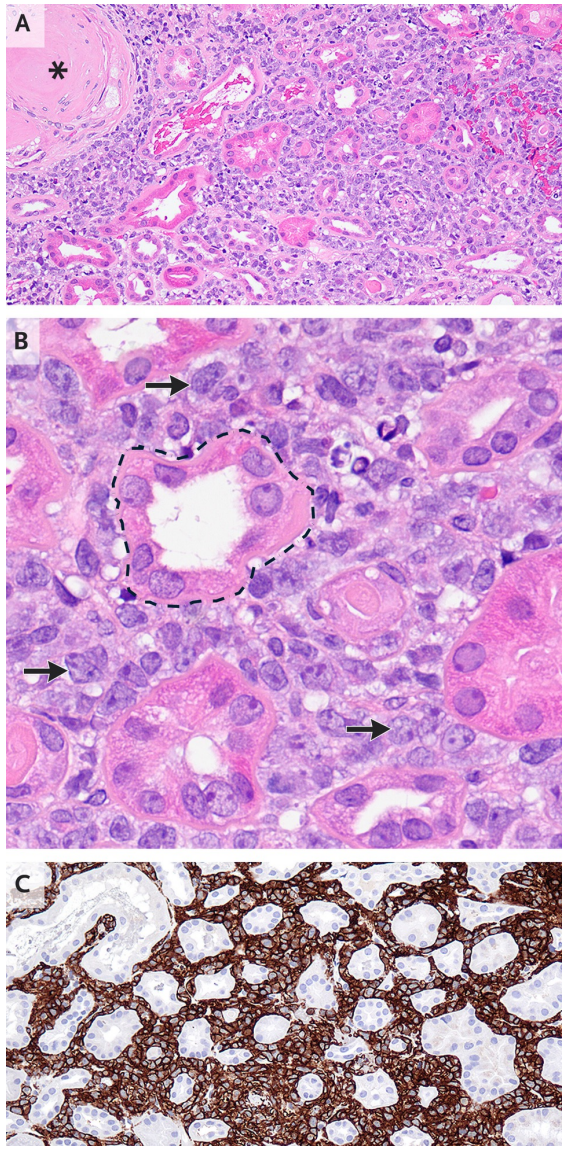
A random urinary calcium level was 29.6 mg per deciliter (7.40 mmol per liter), with a urinary creatinine level of 114.2 mg per deciliter (10,095 µmol per liter), for a ratio of 0.26 (normal value, <0.22); the microalbumin level was 157 mg per deciliter (normal value, <2). Urinalysis revealed a normal pH, specific gravity of 1.014 (normal range, 1.003 to 1.035), 3+ glucose, 2+ protein, 1+ blood, and 1+ leukocyte esterase. Urinary sediment revealed 3+ bacteria, with 26 white cells per high-power field (normal range, 0 to 9), 7 red cells per high-power field (normal range, 0 to 2), 75 hyaline casts per low-power field (normal value, 0, 1, or 2), and 6 granular casts per low-power field (normal value, 0). A urine culture grew more than 100,000 colony-forming units of mixed flora per milliliter.

The patient received continuous normal saline with intravenous furosemide in order to reach a urine-output level of 150 ml of urine per hour with euvolemia, one dose (120 mg) of denosumab administered subcutaneously, and calcitonin (4 U per kilogram of body weight) administered subcutaneously every 12 hours for four doses. Acute kidney injury precluded bisphosphonate use.




**Samples from CT-Guided Core Biopsy of a Lesion in the Right Iliac Crest.**

Hematoxylin and eosin staining showed a diffuse infiltrate of large atypical lymphoid cells (Panel A) with ovoid-to-irregular nuclei, vesicular chromatin, and prominent nucleoli (Panel B; arrows point to example atypical lymphoid cells). Panel B shows magnification at six times that in Panel A. Immunohistochemical staining showed that the lymphoid cells were diffusely positive for the B-cell marker CD20 (Panel C). The percentage of cells staining for Ki-67, a marker of proliferation, was markedly increased (>90% of cells) (Panel D), a finding consistent with an aggressive cancer. Panels C and D both show magnification at four times that in Panel A. Additional immunohistochemical markers (not shown) stained the atypical cells diffusely positive for paired box 5 (PAX5), multiple myeloma oncogene 1 (MUM1), B-cell lymphoma 6 (BCL6), and B-cell lymphoma 2 (BCL2). A subset of cells (30 to 40%) stained positive for myelocytomatosis proto-oncogene (MYC). The cells stained negative for CD3, CD5, CD10, CD34, terminal deoxynucleotidyl transferase (TdT), CD138, Epstein–Barr virus–encoded RNAs detected by in situ hybridization, cyclin D1, and CD30. Fluorescence in situ hybridization (not shown) did not detect an *MYC* gene rearrangement.



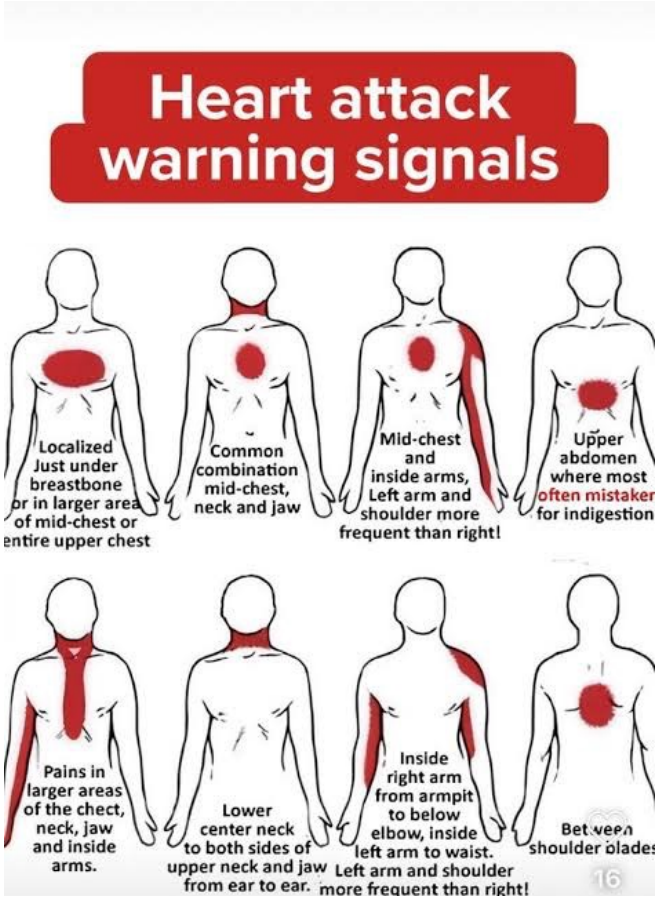

**Kidney-Biopsy Sample.**

Hematoxylin and eosin staining of a kidney-biopsy sample showed global glomerulosclerosis (Panel A, asterisk) and an interstitial atypical lymphoid infiltrate. The cells infiltrating between the tubules were identical to those seen in the previous bone biopsy with ovoid to irregular nuclei, vesicular chromatin, and prominent nucleoli (Panel B; arrows point to example neoplastic cells, and the dashed line marks an example tubule). Panel B shows magnification at four times that in Panel A. Immunohistochemical staining indicated lymphoid cells diffusely positive for CD20 (Panel C); positive for BCL6, BCL2, and MUM1 (not shown); and negative for CD10 (not shown). Panel C shows magnification at two times that in Panel A.

**Commentary**

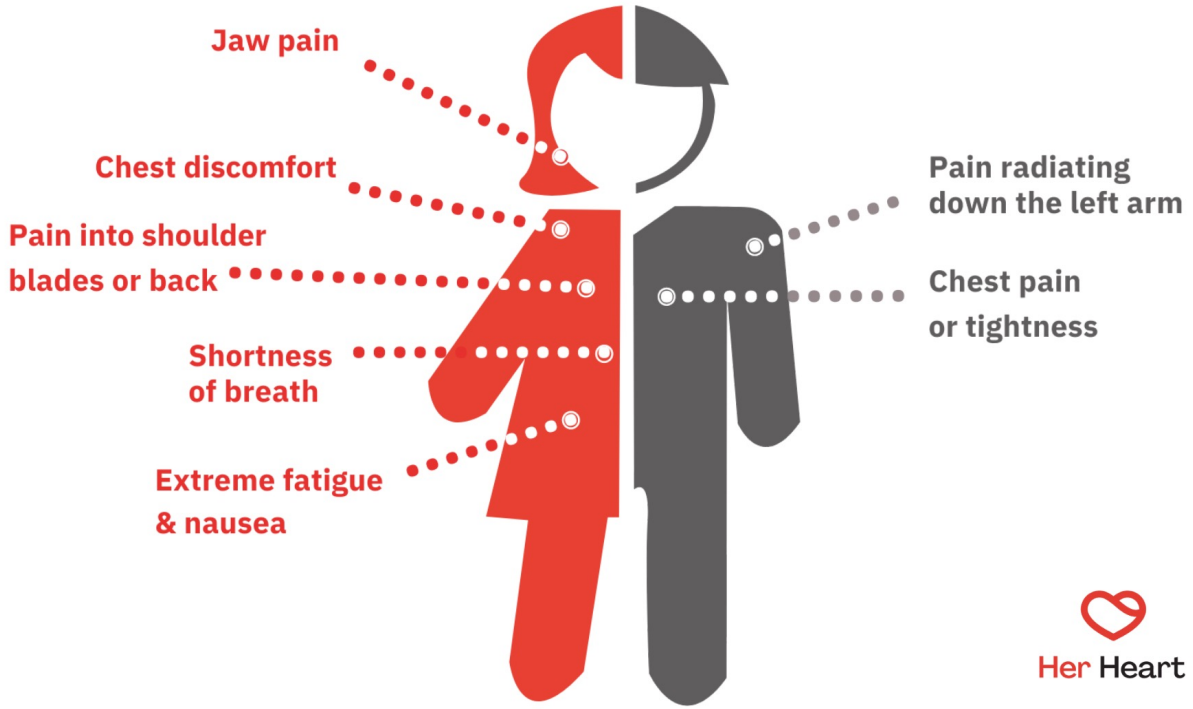
This patient presented with constitutional, abdominal, and neurologic signs and symptoms of severe hypercalcemia. Low levels of vitamin D and PTH aroused suspicion for a malignant cause, with imaging revealing diffuse lytic bone lesions and biopsy confirming DLBCL in bone and kidney. Hypercalcemia occurs in 2 to 30% of patients with cancer. Severe hypercalcemia — as indicated by a total serum calcium level exceeding 14 mg per deciliter (3.50 mmol per liter) — represents a medical emergency. Severe hypercalcemia typically manifests with cognitive and renal dysfunction and may be associated with life-threatening cardiac arrhythmias. Expert guidelines recommend prompt management, including isotonic fluid repletion to promote calciuresis and loop diuretics to prevent volume overload in patients with cardiac or renal dysfunction. Calcitonin is recommended early for patients with severe hypercalcemia; it inhibits bone resorption and promotes renal calcium excretion, rapidly reducing serum calcium levels within 4 to 6 hours after administration, but tachyphylaxis limits efficacy to approximately 2 days. Intravenous bisphosphonate therapy or denosumab provides longer-term suppression of bone resorption and sustained calcium reduction and is recommended for moderate-to-severe or symptomatic cancer-associated hypercalcemia. Denosumab is preferred over bisphosphonates in patients with advanced renal dysfunction (e.g., eGFR, <35 ml per minute per 1.73 $m^2$) in order to avoid worsening kidney injury.

THE LANCET




# Know the difference

Heart attack warning signs differ between women and men

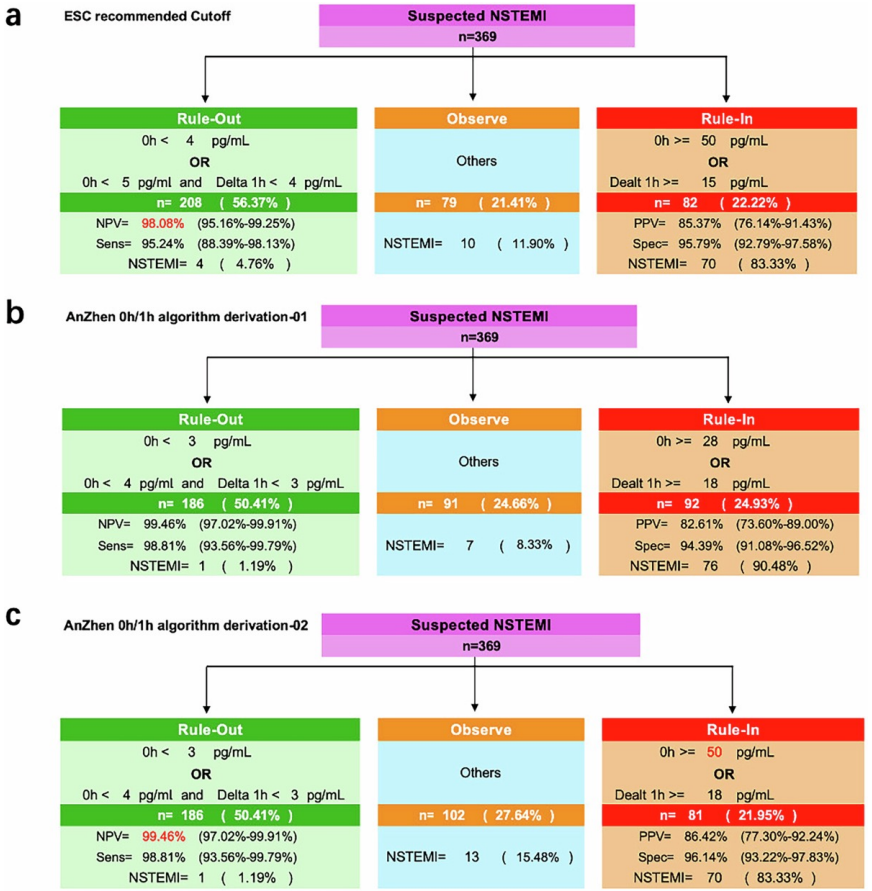



Her Heart

Das **0/1-Stunden-Protokoll** und das **0/3-Stunden-Protokoll** sind beschleunigte Diagnostikpfade (Accelerated Diagnostic Pathways, ADPs) der Europäischen Gesellschaft für Kardiologie (ESC) zum schnellen Ausschluss oder Nachweis eines akuten Myokardinfarkts (Herzinfarkts) mittels hochsensitiver Troponin-Bestimmung (hs-cTn) bei Patienten mit unklaren Brustschmerzen.

**Die wichtigsten Unterschiede im Vergleich**

- **Zeitintervall der Blutentnahme:**
  - **0/1-Stunden-Pfad:** Erneute Troponin-Messung bereits **1 Stunde** nach der Baseline-Messung (0 h).
  - **0/3-Stunden-Pfad:** Erneute Troponin-Messung erst nach **3 Stunden**.



# Safety and efficacy of the 0/1 h pathway for myocardial infarction in the emergency department: an international, pragmatic, stepped-wedge, cluster-randomised, controlled trial

0/1 is no worse than 0/3, but time in ER is no different

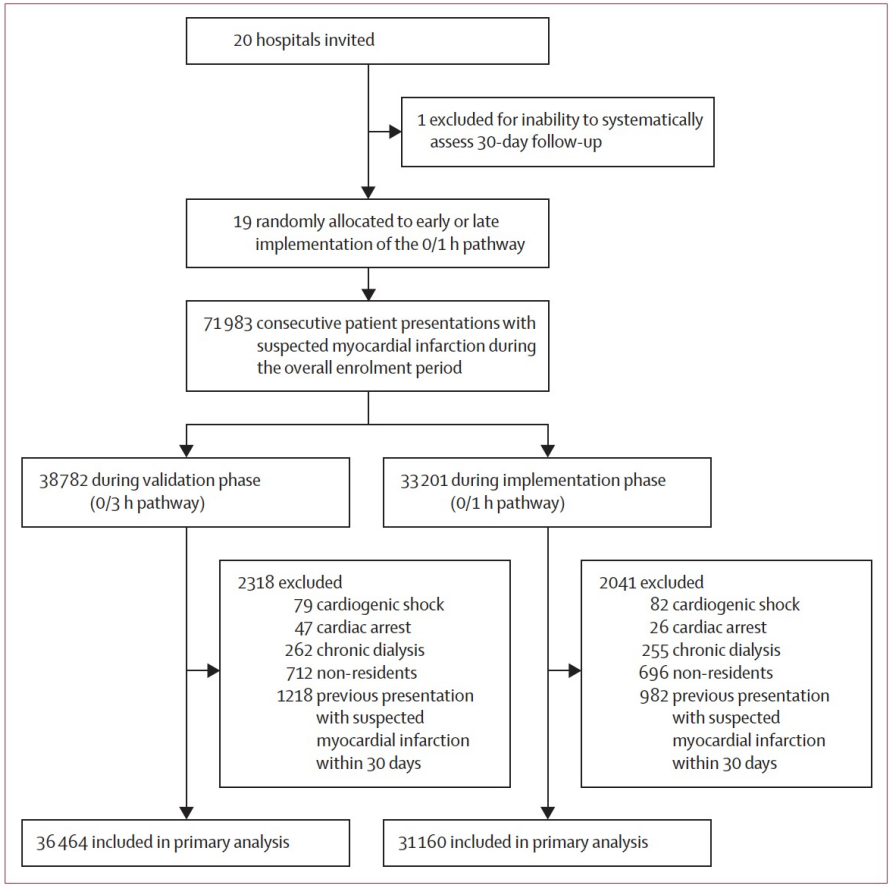

## Summary

**Background** The evaluation of patients with suspected myocardial infarction relies on serial measurements of high-sensitivity cardiac troponin. We aimed to evaluate the safety and efficacy of implementing the guideline-recommended 0/1 h pathway, compared with a 0/3 h pathway, in hospitals that had not yet adopted the newer strategy.

**Methods** PRESC1SE-MI was an international, pragmatic, stepped-wedge, cluster-randomised, controlled, masked-endpoint trial at 19 hospitals in ten countries. The study included consecutive adults presenting to the emergency department with acute non-traumatic chest discomfort and suspected myocardial infarction. Hospitals using a 0/3 h pathway (blood draws at 0 h and 3 h) as standard care were randomly allocated to implement the 0/1 h pathway (blood draws at 0 h and 1 h) after 6 months (early implementation) or 12 months (late implementation). The trial was designed to test the non-inferiority of the 0/1 h pathway for safety and its superiority for efficacy. The non-inferiority margin was set at an odds ratio of 1·3. Analyses were done in the full analysis set. The coprimary safety outcome was a composite of death from any cause or new type 1 myocardial infarction within 30 days, and the coprimary efficacy outcome was emergency department length of stay. This trial is registered with ClinicalTrials.gov, NCT05649384, and is active but no longer enrolling.

**Findings** Between Dec 1, 2020, and Dec 31, 2024, 71983 consecutive patient presentations were screened, of which 67624 (93·9%) met the eligibility criteria and comprised the full analysis set. Median age was 59 years (IQR 46–73); 29954 (44·3%) patient presentations were in female patients and 37670 (55·7%) were in male patients. 13753 (22·2%) of 62060 patient presentations with available data were in patients with known coronary artery disease, and 5855 (8·7%) patient presentations had an adjudicated index diagnosis of myocardial infarction. Overall, 36464 patient presentations were managed with a 0/3 h pathway and 31160 with the 0/1 h pathway. Death from any cause or new type 1 myocardial infarction occurred in 454 (1·2%) patient presentations in the 0/3 h group and in 341 (1·1%) patient presentations in the 0/1 h group (adjusted odds ratio 0·93 [95% CI 0·77–1·13]; $p_{non\text{-}inferiority}$=0·0004). The median emergency department length of stay was 309 min (IQR 203–470) in the 0/3 h pathway and 309 min (207–474) in the 0/1 h pathway (ratio of adjusted median times 1·00 [95% CI 0·97–1·02]; two-sided p=0·65).

**Interpretation** Implementation of the 0/1 h pathway met the prespecified non-inferiority criterion for the 30-day composite safety outcome but did not shorten emergency department length of stay compared with the 0/3 h pathway. In this setting, implementation of the 0/1 h pathway alone should therefore not be expected to improve emergency department throughput.




| | 0/3 h pathway (n=36 464) | 0/1 h pathway (n=31 160) |
|---|---|---|
| **Demographic data** | | |
| Age, years | 59 (46–73) | 59 (46–73) |
| Sex | | |
| Female | 16 272 (44·6%) | 13 682 (43·9%) |
| Male | 20 192 (55·4%) | 17 478 (56·1%) |
| Medical history | | |
| Brought in by ambulance | 11 522/33 277 (34·6%) | 7997/25 625 (31·2%) |
| Known coronary artery disease | 7782/33 841 (23·0%) | 5971/28 219 (21·2%) |
| Previous myocardial infarction | 5017/36 464 (13·8%) | 3905/31 160 (12·5%) |
| Previous stroke | 1538/36 464 (4·2%) | 1147/31 159 (3·7%) |
| Diabetes | 6338/33 273 (19·0%) | 4441/25 625 (17·3%) |
| Chronic kidney disease | 2825/36 464 (7·7%) | 1878/31 160 (6·0%) |
| Clinical status | | |
| Heart rate, beats/min* | 82 (20) | 81 (19) |
| Blood pressure, mm Hg | | |
| Systolic† | 141 (27) | 140 (24) |
| Diastolic‡ | 82 (15) | 81 (15) |
| Ischaemia on electrocardiogram | 4615/35 903 (12·9%) | 3634/30 712 (11·8%) |
| Index event myocardial infarction | 3215/36 464 (8·8%) | 2640/31 160 (8·5%) |
| **Setting** | | |
| Emergency department visit | | |
| First presentation | 34 548 (94·7%) | 28 029 (90·0%) |
| Recurrent presentation after >30 days§ | 1916 (5·3%) | 3131 (10·0%) |
| Season | | |
| Spring | 10 431 (28·6%) | 10 209 (32·8%) |
| Summer | 7064 (19·4%) | 5050 (16·2%) |
| Autumn | 7902 (21·7%) | 6061 (19·5%) |
| Winter | 11 067 (30·4%) | 9840 (31·6%) |
| Region | | |
| Europe | 31 412 (86·1%) | 27 620 (88·6%) |
| North America | 3560 (9·8%) | 1912 (6·1%) |
| Asia | 1155 (3·2%) | 742 (2·4%) |
| Australia | 337 (0·9%) | 886 (2·8%) |
| Cardiac troponin assay type | | |
| T | 14 602 (40·0%) | 15 064 (48·3%) |
| I | 21 862 (60·0%) | 16 096 (51·7%) |
| Upper reference limit | | |
| Uniform | 18 398 (50·5%) | 17 897 (57·4%) |
| Sex-specific | 18 066 (49·5%) | 13 263 (42·6%) |

Data are median (IQR), n (%), n/N (%), or mean (SD). The full analysis set included all patient presentations during the validation and implementation phases. *Data were available for 64 636 patient presentations (34 967 in the 0/3 h group and 29 669 in the 0/1 h group). †Data were available for 64 650 patient presentations (34 826 in the 0/3 h group and 29 824 in the 0/1 h group). ‡Data were available for 64 635 patient presentations (34 812 in the 0/3 h group and 29 823 in the 0/1 h group). §The second presentation occurred at a mean 101 days (SD 67) after the first in the 0/3 h group and 211 days (SD 145) in the 0/1 h group. The mean interval relates to the second eligible presentation among patients with more than one eligible presentation.

***Table 1:*** **Characteristics of patient presentations at baseline**

| | 0/3 h pathway (n=36 464) | 0/1 h pathway (n=31 160) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| **Coprimary outcomes** | | | | |
| Death from any cause or new type 1 myocardial infarction* | 454 (1·2%) | 341 (1·1%) | 0·93 (0·77–1·13) | 0·0004 (non-inferiority) |
| Emergency department length of stay, min† | 309 (203–470) | 309 (207–474) | 1·00 (0·97–1·02) | 0·65 (superiority) |
| **Secondary and additional outcomes** | | | | |
| Death from any cause* | 383 (1·1%) | 255 (0·8%) | 0·84 (0·67–1·06) | .. |
| New type 1 myocardial infarction* | 76 (0·2%) | 92 (0·3%) | 1·55 (1·07–2·24) | .. |
| Readmission for suspected myocardial infarction‡ | 914 (2·5%) | 756 (2·4%) | 0·97 (0·80–1·18) | .. |
| Outpatient management | 25 935 (71·1%) | 23 085 (74·1%) | .. | .. |
| Death from cardiovascular causes§ | 202 (0·6%) | 140 (0·4%) | .. | .. |
| Patient satisfaction¶ | 90 (80–100) | 90 (80–100) | .. | .. |
| Effectiveness of rule-in, min‖ | 476 (95–1694) | 496 (99–1606) | .. | .. |
| Effectiveness of rule-out, min** | 308 (203–469) | 309 (208–472) | .. | .. |
| Emergency department physician satisfaction†† | | | | |
| Easy to implement, good evidence | 4·0 (0·8) | 4·0 (0·8) | .. | .. |
| Satisfied | 3·7 (0·9) | 4·0 (0·9) | .. | .. |
| Efficient | 3·3 (0·9) | 4·0 (0·9) | .. | .. |
| Enough time for tasks | 3·0 (1·1) | 2·9 (1·1) | .. | .. |
| More work with 0/1 h | .. | 2·3 (1·0) | .. | .. |
| Emergency department nurse satisfaction†† | | | | |
| Easy to implement, good evidence | 4·0 (0·8) | 4·0 (0·8) | .. | .. |
| Satisfied | 3·7 (1·0) | 3·9 (0·9) | .. | .. |
| Efficient | 3·4 (1·1) | 3·8 (1·1) | .. | .. |
| Enough time for my tasks | 3·0 (1·1) | 2·8 (1·2) | .. | .. |
| More work with 0/1 h | .. | 2·8 (1·3) | .. | .. |
| Feasibility second hs-cTn blood draw obtained‡‡ | .. | 10 965 (62·8%) | .. | .. |
| Feasibility second hs-cTn blood draw obtained within 40–100 min‡‡ | .. | 5772 (33·1%) | .. | .. |
| Feasibility second hs-cTn blood draw obtained within 40–80 min‡‡ | .. | 4383 (25·1%) | .. | .. |

Data are n (%), median (IQR), or mean (SD), unless otherwise specified. The full analysis set included all patient presentations during the validation and implementation phases. All clinical outcomes are reported at 30 days of follow-up. The models were adjusted for age, sex, season, linear time trend, and site. hs-cTn=high-sensitivity cardiac troponin. *Could not be analysed in 58 patient presentations in which patients died within 12 h (32 in the 0/3 h group and 26 in the 0/1 h group), which were considered as index events and not trial outcomes, and in 14 patient presentations without 30-day follow-up data (four in the 0/3 h group and ten in the 0/1 h group). †Ratio of the adjusted median times under the 0/1 h pathway compared with the 0/3 h pathway (95% Wald CI); data not available in four patient presentations (three in the 0/3 h group and one in the 0/1 h group). ‡Defined as all hospitalisations for cardiac causes to screen for myocardial infarction as a possible cause. Could not be analysed in 58 patient presentations in which patients died within 12 h (32 in the 0/3 h group and 26 in the 0/1 h group), which were considered as index events and not trial outcomes, and in 14 patient presentations without 30-day follow-up data (four in the 0/3 h group and ten in the 0/1 h group). §Post-hoc descriptive analysis. ¶Self-assessed on a visual analogue scale, range 0–100, with higher values indicating higher satisfaction; data were available for 20 885 patient presentations (10 882 in the 0/3 h group and 10 003 in the 0/1 h group). ‖Defined as the time from presentation to coronary angiography in patient presentations ultimately diagnosed with type 1 myocardial infarction; data were available for 3655 patient presentations (2059 in the 0/3 h group and 1596 in the 0/1 h group). **Defined as time from presentation to discharge in patient presentations ultimately diagnosed with non-cardiac disease; data were available for 27 915 patient presentations (15 231 in the 0/3 h group and 12 684 in the 0/1 h group). ††Likert scale from 1 to 5 for the answers 1=strongly disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, or 5=strongly agree, sent via anonymised replies to a survey. Data available for emergency department physicians (240 for 0/3 h pathways and 196 for the 0/1 h pathway) and emergency department nurses (322 for 0/3 h pathways and 251 for the 0/1 h pathway). ‡‡Proportion of all patient presentations that formally required a second hs-cTn blood draw with the 0/1 h pathway (n=17 448). It was done at 1 h or earlier in 2401 (14%) patient presentations.

***Table 2:*** **Primary and secondary outcomes**

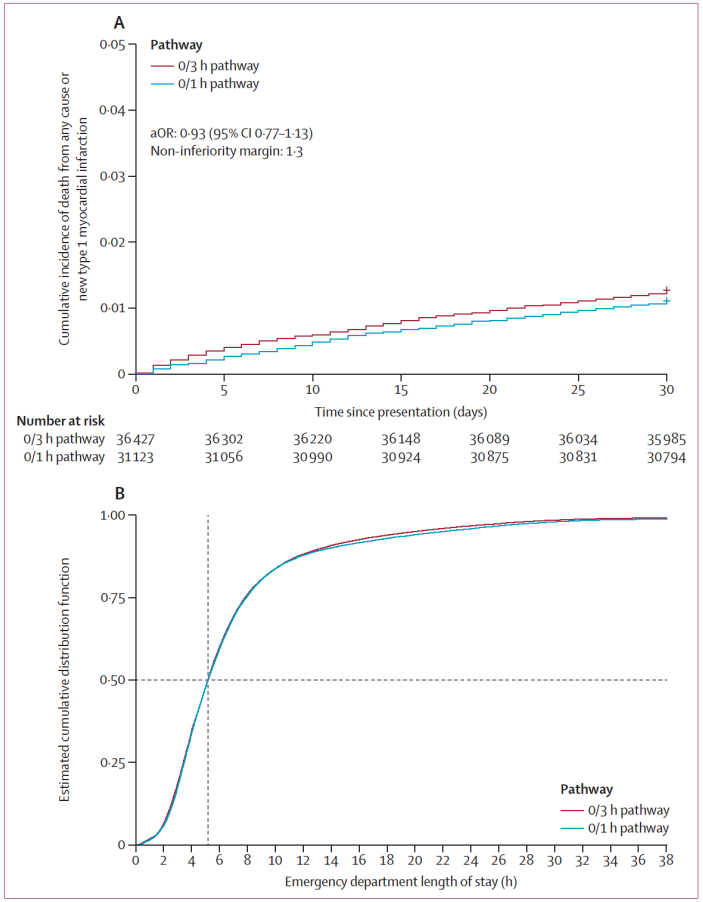



***Figure 2:*** **Coprimary outcomes**

(A) Safety: cumulative incidence of death from any cause or new type 1 myocardial infarction within 30 days. There was no censoring within 30 days among patient presentations included in the analysis. 74 patient presentations were not included: 58 in which patients died within 12 h while continuously in hospital (32 in the 0/3 h group and 26 in the 0/1 h group), and these deaths were considered index events rather than trial outcomes; 14 without 30-day follow-up data (four in the 0/3 h group and ten in the 0/1 h group); and two (one in each group) in which the date of new type 1 myocardial infarction was unknown. Unadjusted Kaplan–Meier cumulative incidence curves are shown for each group. The treatment effect was reported as an odds ratio, as specified in the statistical analysis plan. (B) Efficacy: cumulative distribution curve of emergency department length of stay. Data were not available in four patient presentations (three in the 0/3 h group and one in the 0/1 h group). Unadjusted estimated cumulative distribution functions are shown for each group. aOR=adjusted odds ratio.

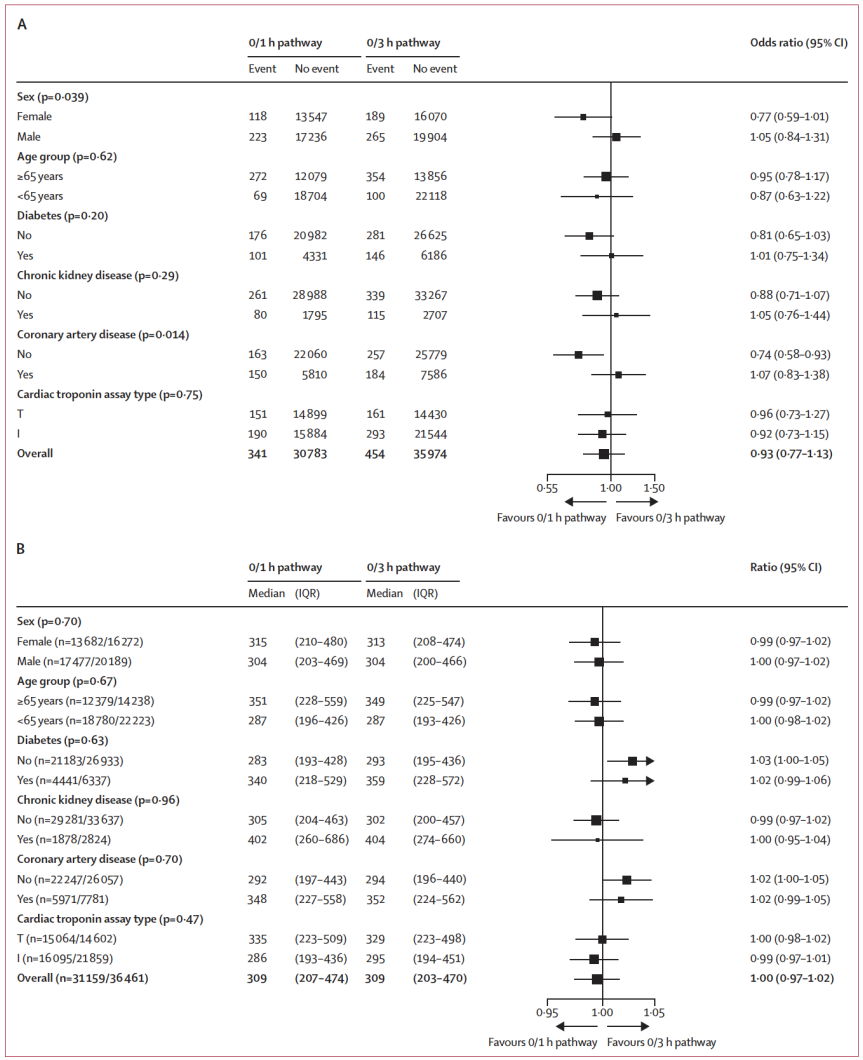



*Figure 3*: **Subgroup analyses**
Forest plot of prespecified subgroup analyses for (A) the coprimary safety outcome of death from any cause or new type 1 myocardial infarction within 30 days and (B) the coprimary efficacy outcome of emergency department length of stay.

## Implications of all the available evidence

The results of PRESC1SE-MI show that implementation of the 0/1 h pathway met the prespecified non-inferiority criterion for the 30-day composite safety outcome in late-adopting hospitals across diverse countries and health-care systems but did not shorten emergency department length of stay. The divergence in the direction of both components of the safety outcome requires further study. Health-care providers should be aware of the challenges and implementation barriers when considering adoption of the 0/1 h pathway in clinical practice.

0/1 is no worse than 0/3, but time in ER is no different

# Performance of 0/1 h versus 0/3 h pathways in patients with suspected myocardial infarction: a systematic review and individual participant data meta-analysis of randomised controlled trials


## Summary

**Background** In patients with suspected myocardial infarction, the 0/1 h pathway (blood draws at 0 h and 1 h) is recommended in current guidelines for early risk stratification. However, individual trials used different safety outcomes, and efficacy outcomes were inconclusive or not assessed. We conducted a systematic review and individual participant data meta-analysis of all randomised controlled trials to synthesise the totality of the evidence, assess heterogeneity across trials, and evaluate clinically relevant outcomes using harmonised definitions across trials.

**Methods** In this systematic review and individual participant data meta-analysis, we searched PubMed, Cochrane Central Register of Controlled Trials, Scopus, and the International Clinical Trials Registry Platform from inception to July 6, 2026, without language restrictions, for randomised trials comparing the safety and efficacy of 0/1 h versus 0/3 h pathways (blood draws at 0 h and 3 h, ie, standard care). Individual participant data were obtained and outcome definitions were harmonised. The primary analysis used a two-stage random-effects meta-analysis. After receipt of the individual participant data but before data harmonisation or analysis, the primary safety outcome was refined to a composite of all-cause death or new type 1 myocardial infarction within 30 days, from the originally specified composite of all-cause death or any new myocardial infarction. The primary efficacy outcomes were emergency department length of stay and direct discharge from the emergency department. This meta-analysis is registered with PROSPERO (CRD420261383452).

**Findings** Our systematic review identified five randomised trials, all of which provided individual participant data. Among these, the definition of the primary safety outcome varied, and in four trials emergency department length of stay was not reported for the whole analysis population. We included 110 933 patient presentations (55 489 managed with the 0/1 h pathway and 55 444 managed with the 0/3 h pathway). Within 30 days, all-cause death or new type 1 myocardial infarction occurred in 446 patient presentations (0·8%) with the 0/1 h pathway versus 562 patient presentations (1·0%) with the 0/3 h pathway (random-effects pooled odds ratio [OR] 0·83 [95% CI 0·45–1·53]; $I^2$=62·9%; $\tau^2$=0·143). Emergency department length of stay was 314 min (IQR 211–481) in the 0/1 h pathway group versus 308 min (209–453) in the 0/3 h pathway group (random-effects pooled geometric mean ratio 1·03 [95% CI 0·85–1·25]; $I^2$=99·2%; $\tau^2$=0·024). Direct discharge from the emergency department occurred in 37 190 patient presentations (67·0%) with the 0/1 h pathway versus 36 485 patient presentations (65·8%) with the 0/3 h pathway (random-effects pooled OR 1·31 [95% CI 0·79–2·16]; $I^2$=97·8%; $\tau^2$=0·156).

**Interpretation** Across the available randomised trials, short-term adverse event rates were low with both pathways, but the pooled safety estimate remained imprecise. On average, earlier cardiac troponin retesting did not reduce emergency department length of stay or clearly increase direct discharge, and substantial between-study heterogeneity indicates that treatment effects might not translate uniformly across health-care systems. For hospitals considering transitioning from a 0/3 h to a 0/1 h pathway, implementation decisions should take broader diagnostic and organisational considerations into account.



**Funding** Swiss National Science Foundation, Swiss Heart Foundation, University Hospital Basel, University of Basel, and Foundation for Cardiovascular Research Basel.

| | Total (N=110 933) | RAPID-TnT[19] (n=3288) | RACE-IT[21] (n=32 609) | DROP-Asian ACS[18] (n=3869) | MACROS-2[20] (n=3543) | PRESC1SE-MI[22] (n=67 624) |
|---|---|---|---|---|---|---|
| Pathway | | | | | | |
| 0/1 h | 55 489 (50·0%) | 1646 (50·0%) | 19 104 (58·6%) | 1810 (46·8%) | 1769 (49·9%) | 31 160 (46·1%) |
| 0/3 h | 55 444 (50·0%) | 1642 (50·0%) | 13 505 (41·4%) | 2059 (53·2%) | 1774 (50·1%) | 36 464 (53·9%) |
| Age, years | 59·0 (46·0–72·0) | 59·0 (49·0–70·0) | 59·0 (45·0–71·0) | 62·0 (51·0–71·0) | 60·0 (49·0–70·0) | 59·0 (46·0–73·0) |
| Sex | | | | | | |
| Female | 53 020/110 928 (47·8%) | 1539/3288 (46·8%) | 18 705/32 604 (57·4%) | 1167/3869 (30·2%) | 1655/3543 (46·7%) | 29 954/67 624 (44·3%) |
| Male | 57 908/110 928 (52·2%) | 1749/3288 (53·2%) | 13 899/32 604 (42·6%) | 2702/3869 (69·8%) | 1888/3543 (53·3%) | 37 670/67 624 (55·7%) |
| NA | 5 | 0 | 5 | 0 | 0 | 0 |
| Previous myocardial infarction | | | | | | |
| No | 99 234/110 933 (89·5%) | 2957/3288 (89·9%) | 31 420/32 609 (96·4%) | 3164/3869 (81·8%) | 2991/3543 (84·4%) | 58 702/67 624 (86·8%) |
| Yes | 11 699/110 933 (10·5%) | 331/3288 (10·1%) | 1189/32 609 (3·6%) | 705/3869 (18·2%) | 552/3543 (15·6%) | 8922/67 624 (13·2%) |
| Previous stroke | | | | | | |
| No | 72 007/75 035 (96·0%) | NA | NA | 3743/3869 (96·7%) | 3326/3543 (93·9%) | 64 938/67 623 (96·0%) |
| Yes | 3028/75 035 (4·0%) | NA | NA | 126/3869 (3·3%) | 217/3543 (6·1%) | 2685/67 623 (4·0%) |
| NA | 35 898 | 3288 | 32 609 | 0 | 0 | 1 |
| Known coronary artery disease | | | | | | |
| No | 77 288/94 669 (81·6%) | NA | 28 981/32 609 (88·9%) | NA | NA | 48 307/62 060 (77·8%) |
| Yes | 17 381/94 669 (18·4%) | NA | 3628/32 609 (11·1%) | NA | NA | 13 753/62 060 (22·2%) |
| NA | 16 264 | 3288 | 0 | 3869 | 3543 | 5564 |
| Arterial hypertension | | | | | | |
| No | 56 237/101 913 (55·2%) | 2383/2994 (79·6%) | 17 006/32 609 (52·2%) | 1392/3869 (36·0%) | 2047/3543 (57·8%) | 33 409/58 898 (56·7%) |
| Yes | 45 676/101 913 (44·8%) | 611/2994 (20·4%) | 15 603/32 609 (47·8%) | 2477/3869 (64·0%) | 1496/3543 (42·2%) | 25 489/58 898 (43·3%) |
| NA | 9020 | 294 | 0 | 0 | 0 | 8726 |
| Dyslipidaemia | | | | | | |
| No | 70 459/102 207 (68·9%) | 1853/3288 (56·4%) | 22 197/32 609 (68·1%) | 1686/3869 (43·6%) | 2768/3543 (78·1%) | 41 955/58 898 (71·2%) |
| Yes | 31 748/102 207 (31·1%) | 1435/3288 (43·6%) | 10 412/32 609 (31·9%) | 2183/3869 (56·4%) | 775/3543 (21·9%) | 16 943/58 898 (28·8%) |
| NA | 8726 | 0 | 0 | 0 | 0 | 8726 |
| Diabetes | | | | | | |
| No | 81 614/101 913 (80·1%) | 2540/2994 (84·8%) | 25 512/32 609 (78·2%) | 2505/3869 (64·7%) | 2938/3543 (82·9%) | 48 119/58 898 (81·7%) |
| Yes | 20 299/101 913 (19·9%) | 454/2994 (15·2%) | 7097/32 609 (21·8%) | 1364/3869 (35·3%) | 605/3543 (17·1%) | 10 779/58 898 (18·3%) |
| NA | 9020 | 294 | 0 | 0 | 0 | 8726 |
| Smoking status | | | | | | |
| Never smoked | 60 414/98 651 (61·2%) | 1327/3288 (40·4%) | 13 634/29 104 (46·8%) | 2228/3818 (58·4%) | 1555/3543 (43·9%) | 41 670/58 898 (70·7%) |
| Active smoker | 17 691/98 651 (17·9%) | 1154/3288 (35·1%) | 6268/29 104 (21·5%) | 628/3818 (16·4%) | 656/3543 (18·5%) | 8985/58 898 (15·3%) |
| Former smoker | 20 546/98 651 (20·8%) | 807/3288 (24·5%) | 9202/29 104 (31·6%) | 962/3818 (25·2%) | 1332/3543 (37·6%) | 8243/58 898 (14·0%) |
| NA | 12 282 | 0 | 3505 | 51 | 0 | 8726 |
| Family history of coronary artery disease | | | | | | |
| No | 59 770/69 007 (86·6%) | 1287/3232 (39·8%) | NA | 2401/3334 (72·0%) | 2157/3543 (60·9%) | 53 925/58 898 (91·6%) |
| Yes | 9237/69 007 (13·4%) | 1945/3232 (60·2%) | NA | 933/3334 (28·0%) | 1386/3543 (39·1%) | 4973/58 898 (8·4%) |
| NA | 41 926 | 56 | 32 609 | 535 | 0 | 8726 |
| Ischaemia on ECG | | | | | | |
| No | 67 186/77 196 (87·0%) | 3254/3287 (99·0%) | NA | 2977/3763 (79·1%) | 2589/3531 (73·3%) | 58 366/66 615 (87·6%) |
| Yes | 10 010/77 196 (13·0%) | 33/3287 (1·0%) | NA | 786/3763 (20·9%) | 942/3531 (26·7%) | 8249/66 615 (12·4%) |
| NA | 33 737 | 1 | 32 609 | 106 | 12 | 1009 |

(Table 1 continues on next page)

| | Total (N=110 933) | RAPID-TnT[19] (n=3288) | RACE-IT[21] (n=32 609) | DROP-Asian ACS[18] (n=3869) | MACROS-2[20] (n=3543) | PRESC1SE-MI[22] (n=67 624) |
|---|---|---|---|---|---|---|
| (Continued from previous page) | | | | | | |
| Estimated GFR, mL/min per 1·73 m² | 89·0 (69·0–104·0) | 85·0 (72·0–99·0) | 87·0 (65·0–104·0) | 61·6 (48·1–74·5) | 83·0 (68·0–90·0) | 93·2 (75·3–106·3) |
| Troponin assay type | | | | | | |
| hs-cTnT | 40 366/110 933 (36·4%) | 3288/3288 (100%) | 0/32 609 | 3869/3869 (100%) | 3543/3543 (100%) | 29 666/67 624 (43·9%) |
| hs-cTnI | 70 567/110 933 (63·6%) | 0/3288 | 32 609/32 609 (100%) | 0/3869 | 0/3543 | 37 958/67 624 (56·1%) |
| Use of sex-specific cutoffs | | | | | | |
| Uniform | 79 604/110 933 (71·8%) | 3288/3288 (100%) | 32 609/32 609 (100%) | 3869/3869 (100%) | 3543/3543 (100%) | 36 295/67 624 (53·7%) |
| Sex-specific | 31 329/110 933 (28·2%) | 0/3288 | 0/32609 | 0/3869 | 0/3543 | 31 329/67 624 (46·3%) |
| Season | | | | | | |
| Spring | 23 867/110 933 (21·5%) | 1055/3288 (32·1%) | 468/32 609 (1·4%) | 801/3869 (20·7%) | 903/3543 (25·5%) | 20 640/67 624 (30·5%) |
| Summer | 23 059/110 933 (20·8%) | 791/3288 (24·1%) | 8288/32 609 (25·4%) | 944/3869 (24·4%) | 922/3543 (26·0%) | 12 114/67 624 (17·9%) |
| Autumn | 28 524/110 933 (25·7%) | 778/3288 (23·7%) | 11 901/32 609 (36·5%) | 1063/3869 (27·5%) | 819/3543 (23·1%) | 13 963/67 624 (20·6%) |
| Winter | 35 483/110 933 (32·0%) | 664/3288 (20·2%) | 11 952/32 609 (36·7%) | 1061/3869 (27·4%) | 899/3543 (25·4%) | 20 907/67 624 (30·9%) |

Data are n (%), median (IQR), n/N (%), or n. Cells marked NA indicate that the variable or information was not collected as part of the individual trial. ECG=electrocardiogram. GFR=glomerular filtration rate. hs-cTnI=high-sensitivity cardiac troponin I. hs-cTnT=high-sensitivity cardiac troponin T. NA=not available.

***Table 1:*** **Trial-level population characteristics**

| | Total (n=110 933) | 0/3 h pathway (n=55 444) | 0/1 h pathway (n=55 489) |
|---|---|---|---|
| Age, years | 59·0 (46·0–72·0) | 59·0 (46·0–72·0) | 59·0 (46·0–72·0) |
| Sex | | | |
| Female | 53 020/110 928 (47·8%) | 26 214/55 443 (47·3%) | 26 806/55 485 (48·3%) |
| Male | 57 908/110 928 (52·2%) | 29 229/55 443 (52·7%) | 28 679/55 485 (51·7%) |
| NA | 5 | 1 | 4 |
| Previous myocardial infarction | | | |
| No | 99 234/110 933 (89·5%) | 49 026/55 444 (88·4%) | 50 208/55 489 (90·5%) |
| Yes | 11 699/110 933 (10·5%) | 6418/55 444 (11·6%) | 5281/55 489 (9·5%) |
| Previous stroke | | | |
| No | 72 007/75 035 (96·0%) | 38 570/40 297 (95·7%) | 33 437/34 738 (96·3%) |
| Yes | 3028/75 035 (4·0%) | 1727/40 297 (4·3%) | 1301/34 738 (3·7%) |
| NA | 35 898 | 15 147 | 20 751 |
| Known coronary artery disease | | | |
| No | 77 288/94 669 (81·6%) | 37 989/47 346 (80·2%) | 39 299/47 323 (83·0%) |
| Yes | 17 381/94 669 (18·4%) | 9357/47 346 (19·8%) | 8024/47 323 (17·0%) |
| NA | 16 264 | 8098 | 8166 |
| Arterial hypertension | | | |
| No | 56 237/101 913 (55·2%) | 28 288/52 117 (54·3%) | 27 949/49 796 (56·1%) |
| Yes | 45 676/101 913 (44·8%) | 23 829/52 117 (45·7%) | 21 847/49 796 (43·9%) |
| NA | 9020 | 3327 | 5693 |
| Dyslipidaemia | | | |
| No | 70 459/102 207 (68·9%) | 35 589/52 253 (68·1%) | 34 870/49 954 (69·8%) |
| Yes | 31 748/102 207 (31·1%) | 16 664/52 253 (31·9%) | 15 084/49 954 (30·2%) |
| NA | 8726 | 3191 | 5535 |

(Table 2 continues on next page)

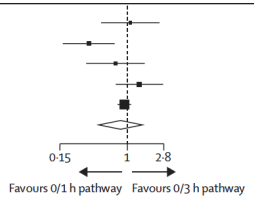
| | Total (N=110 933) | 0/3 h pathway (n=55 444) | 0/1 h pathway (n=55 489) |
|---|---|---|---|
| (Continued from previous page) | | | |
| Diabetes | | | |
| No | 81 614/101 913 (80·1%) | 41 453/52 117 (79·5%) | 40 161/49 796 (80·7%) |
| Yes | 20 299/101 913 (19·9%) | 10 664/52 117 (20·5%) | 9635/49 796 (19·3%) |
| NA | 9020 | 3327 | 5693 |
| Smoking status | | | |
| Never smoked | 60 414/98 651 (61·2%) | 31 957/50 926 (62·8%) | 28 457/47 725 (59·6%) |
| Active smoker | 17 691/98 651 (17·9%) | 8655/50 926 (17·0%) | 9036/47 725 (18·9%) |
| Former smoker | 20 546/98 651 (20·8%) | 10 314/50 926 (20·3%) | 10 232/47 725 (21·4%) |
| NA | 12 282 | 4518 | 7764 |
| Family history of CAD | | | |
| No | 59 770/69 007 (86·6%) | 33 285/38 426 (86·6%) | 26 485/30 581 (86·6%) |
| Yes | 9237/69 007 (13·4%) | 5141/38 426 (13·4%) | 4096/30 581 (13·4%) |
| NA | 41 926 | 17 018 | 24 908 |
| Ischaemia on ECG | | | |
| No | 67 186/77 196 (87·0%) | 35 700/41 310 (86·4%) | 31 486/35 886 (87·7%) |
| Yes | 10 010/77 196 (13·0%) | 5610/41 310 (13·6%) | 4400/35 886 (12·3%) |
| NA | 33 737 | 14 134 | 19 603 |
| Estimated GFR, mL/min per 1·73 m² | 89·0 (69·0–104·0) | 89·0 (69·0–104·0) | 89·0 (69·0–104·1) |
| NA | 26 830 | 14 912 | 11 918 |
| Troponin assay type | | | |
| hs-cTnT | 40 366/110 933 (36·4%) | 20 077/55 444 (36·2%) | 20 289/55 489 (36·6%) |
| hs-cTnI | 70 567/110 933 (63·6%) | 35 367/55 444 (63·8%) | 35 200/55 489 (63·4%) |
| Use of sex-specific cutoffs | | | |
| Uniform | 79 604/110 933 (71·8%) | 37 378/55 444 (67·4%) | 42 226/55 489 (76·1%) |
| Sex-specific | 31 329/110 933 (28·2%) | 18 066/55 444 (32·6%) | 13 263/55 489 (23·9%) |
| Season | | | |
| Spring | 23 867/110 933 (21·5%) | 11 819/55 444 (21·3%) | 12 048/55 489 (21·7%) |
| Summer | 23 059/110 933 (20·8%) | 16 360/55 444 (29·5%) | 6699/55 489 (12·1%) |
| Autumn | 28 524/110 933 (25·7%) | 14 626/55 444 (26·4%) | 13 898/55 489 (25·0%) |
| Winter | 35 483/110 933 (32·0%) | 12 639/55 444 (22·8%) | 22 844/55 489 (41·2%) |

Data are median (IQR), n/N (%), or n. CAD=coronary artery disease. ECG=electrocardiogram. GFR=glomerular filtration rate. hs-cTnI=high-sensitivity cardiac troponin I. hs-cTnT=high-sensitivity cardiac troponin T. NA=not available.

***Table 2:*** **Baseline characteristics of the pooled sample**

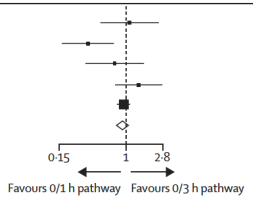
**A**

| | 0/1 h pathway | | 0/3 h pathway | | OR (95% CI) |
|---|---|---|---|---|---|
| | Events | No events | Events | No events | |
| RAPID-TnT | 12 | 1634 | 11 | 1631 | 1·09 (0·48–2·47) |
| RACE-IT | 3 | 19069 | 38 | 13467 | 0·34 (0·16–0·70) |
| DROP-Asian ACS | 37 | 1773 | 44 | 2015 | 0·72 (0·31–1·63) |
| MACROS-2 | 21 | 1748 | 15 | 1759 | 1·41 (0·72–2·74) |
| PRESC1SE-MI | 341 | 30783 | 454 | 35974 | 0·92 (0·76–1·11) |
| **Pooled OR (95% t-distribution-based CI) from random-effects model** | | | | | **0·83 (0·45–1·53)** |
| Heterogeneity: $I^2$=62·9%; $\tau^2$ 0·143; Q* 9·2, p=0·056 | | | | | |



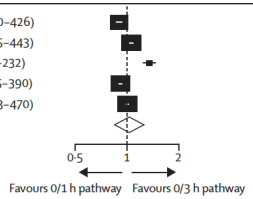

**B**

| | 0/1 h pathway | | 0/3 h pathway | | OR (95% CI) |
|---|---|---|---|---|---|
| | Events | No events | Events | No events | |
| RAPID-TnT | 12 | 1634 | 11 | 1631 | 1·09 (0·48–2·47) |
| RACE-IT | 35 | 19069 | 38 | 13467 | 0·34 (0·16–0·70) |
| DROP-Asian ACS | 37 | 1773 | 44 | 2015 | 0·72 (0·31–1·63) |
| MACROS-2 | 21 | 1748 | 15 | 1759 | 1·41 (0·72–2·74) |
| PRESC1SE-MI | 341 | 30783 | 454 | 35974 | 0·92 (0·76–1·11) |
| **Pooled OR (95% Wald CI) from post-hoc fixed-effect model** | | | | | **0·89 (0·75–1·06)** |
| Heterogeneity: $I^2$=56·5%; Q(df=4)=9·2, p=0·056 | | | | | |



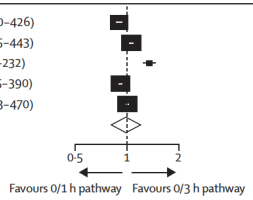

**C**

| | Number of patients/ total number of patients | 0/1 h pathway, median (IQR) | 0/3 h pathway, median (IQR) | Ratio (95% CI) |
|---|---|---|---|---|
| RAPID-TnT | 1646/1642 | 276 (204–384) | 336 (240–426) | 0·90 (0·87–0·93) |
| RACE-IT | 19104/13505 | 347 (234–532) | 309 (225–443) | 1·06 (1·03–1·08) |
| DROP-Asian ACS | 1085/709 | 168 (137–205) | 152 (85–232) | 1·35 (1·24–1·46) |
| MACROS-2 | 1767/1774 | 270 (223–343) | 319 (235–390) | 0·92 (0·89–0·94) |
| PRESC1SE-MI | 31159/36461 | 309 (207–474) | 309 (203–470) | 1·00 (0·98–1·02) |
| **Pooled OR (95% t-distribution-based CI) from random-effects model** | | | | **1·03 (0·85–1·25)** |
| Heterogeneity: $I^2$=99·2%, $\tau^2$=0·024, Q(df=4)=154·56, p<0·0001 | | | | |




**D**

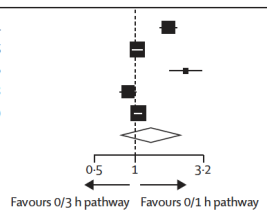
| | Number of patients/ total number of patients | 0/1 h pathway, median (IQR) | 0/3 h pathway, median (IQR) | Ratio (95% CI) |
|---|---|---|---|---|
| RAPID-TnT | 1646/1642 | 276 (204–384) | 336 (240–426) | 0·90 (0·87–0·93) |
| RACE-IT | 19104/13505 | 347 (234–532) | 309 (225–443) | 1·06 (1·03–1·08) |
| DROP-Asian ACS | 1085/709 | 168 (137–205) | 152 (85–232) | 1·35 (1·24–1·46) |
| MACROS-2 | 1767/1774 | 270 (223–343) | 319 (235–390) | 0·92 (0·89–0·94) |
| PRESC1SE-MI | 31159/36461 | 309 (207–474) | 309 (203–470) | 1·00 (0·98–1·02) |
| **Pooled OR (95% Wald CI) from post-hoc fixed-effect model** | | | | **0·99 (0·98–1·00)** |
| Heterogeneity: $I^2$=97·4%, Q(df=4)=154·56, p<0·0001 | | | | |




(Figure 1 continues on next page)

**E**

| | 0/1 h pathway | | 0/3 h pathway | | OR (95% CI) |
|---|---|---|---|---|---|
| | Direct discharge | Not directly discharged | Direct discharge | Not directly discharged | |
| RAPID-TnT | 742 | 904 | 531 | 1111 | 1·76 (1·53–2·04) |
| RACE-IT | 11082 | 8022 | 8070 | 5435 | 1·04 (0·95–1·14) |
| DROP-Asian ACS | 1094 | 716 | 713 | 1346 | 2·36 (1·80–3·11) |
| MACROS-2 | 1187 | 582 | 1236 | 538 | 0·89 (0·77–1·02) |
| PRESC1SE-MI | 23085 | 8075 | 25935 | 10529 | 1·05 (0·99–1·13) |
| **Pooled OR (95% t-distribution-based CI) from random-effects model** | | | | | **1·31 (0·79–2·16)** |
| Heterogeneity: $I^2$=97·8%; $\tau^2$ 0·156; Q(df=4)=82, p<0·0001 | | | | | |




**F**

| | 0/1 h pathway | | 0/3 h pathway | | OR (95% CI) |
|---|---|---|---|---|---|
| | Direct discharge | Not directly discharged | Direct discharge | Not directly discharged | |
| RAPID-TnT | 742 | 904 | 531 | 1111 | 1·76 (1·53–2·04) |
| RACE-IT | 11082 | 8022 | 8070 | 5435 | 1·04 (0·95–1·14) |
| DROP-Asian ACS | 1094 | 716 | 713 | 1346 | 2·36 (1·80–3·11) |
| MACROS-2 | 1187 | 582 | 1236 | 538 | 0·89 (0·77–1·02) |
| PRESC1SE-MI | 23085 | 8075 | 25935 | 10529 | 1·05 (0·99–1·13) |
| **Pooled OR (95% Wald CI) from fixed-effect model** | | | | | **1·11 (1·06–1·17)** |
| Heterogeneity: $I^2$=95·1%, Q(df=4)=82, p<0·0001 | | | | | |

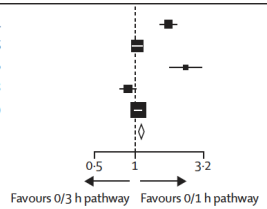
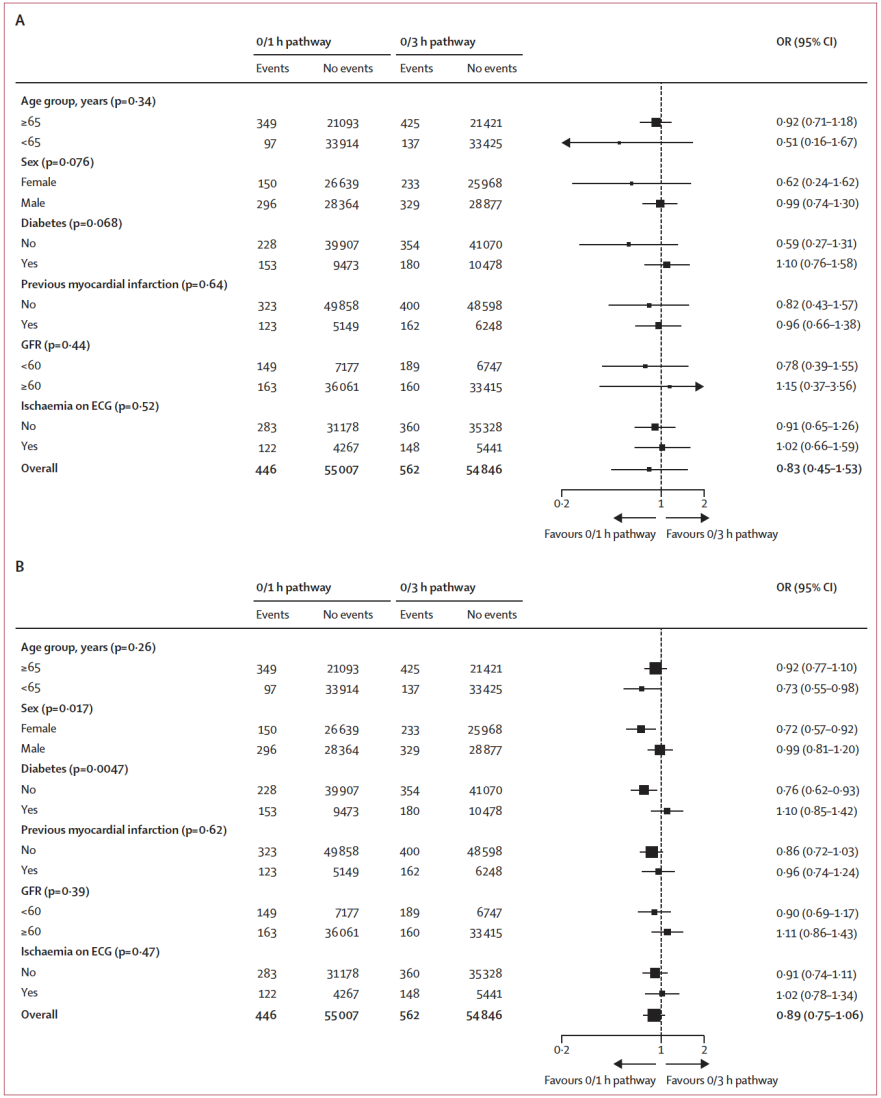



***Figure 1:*** **Forest plots of two-stage meta-analyses for the primary outcomes using random-effects and post-hoc fixed-effect models**
(A) All-cause death or new type 1 myocardial infarction within 30 days, random-effects model. (B) All-cause death or new type 1 myocardial infarction within 30 days, post-hoc fixed-effect model. (C) Median emergency department length of stay in min, random-effects model. (D) Median emergency department length of stay in min, post-hoc fixed-effect model. (E) Direct discharge from the emergency department, random-effects model. (F) Direct discharge from the emergency department, post-hoc fixed-effect model. df=degrees of freesom. OR=odds ratio.

| | 0/3 h pathway (n=55 444) | 0/1 h pathway (n=55 489) | Random-effects model, pooled OR or pooled ratio (95% CI)* | Post-hoc fixed-effect model, pooled OR or geometric mean ratio (95% CI)* |
|---|---|---|---|---|
| **Primary outcomes** | | | | |
| All-cause death or new type 1 MI within 30 days | | | | |
| No | 54 846/55 408 (99·0%) | 55 007/55 453 (99·2%) | 0·83 (0·45–1·53) | 0·89 (0·75–1·06) |
| Yes | 562/55 408 (1·0%) | 446/55 453 (0·8%) | .. | .. |
| NA† | 36 | 36 | .. | .. |
| Median emergency department length of stay, min | 308 (209–453) | 314 (211–481) | .. | .. |
| NA | 1353 | 728 | 1·03 (0·85–1·25) | 0·99 (0·98–1·00) |
| Direct discharge from the emergency department | | | | |
| No | 18 959/55 444 (34·2%) | 18 299/55 489 (33·0%) | 1·31 (0·79– 2·16) | 1·11 (1·06–1·17) |
| Yes | 36 485/55 444 (65·8%) | 37 190/55 489 (67·0%) | .. | .. |
| **Secondary outcomes** | | | | |
| All-cause death within 30 days | | | | |
| No | 54 944/55 408 (99·2%) | 55 129/55 453 (99·4%) | 0·82 (0·65–1·05) | NA |
| Yes | 464/55 408 (0·8%) | 324/55 453 (0·6%) | .. | .. |
| NA | 36 | 36 | .. | .. |
| New type 1 MI within 30 days | | | | |
| No | 55 305/55 408 (99·8%) | 55 325/55 453 (99·8%) | 1·34 (0·89–2·01) | NA |
| Yes | 103/55 408 (0·2%) | 128/55 453 (0·2%) | .. | .. |
| NA | 36 | 36 | .. | .. |
| Cardiovascular death within 30 days | | | | |
| No | 55 174/55 408 (99·6%) | 55 288/55 453 (99·7%) | 0·95 (0·71–1·26) | NA |
| Yes | 234/55 408 (0·4%) | 165/55 453 (0·3%) | .. | .. |
| NA | 36 | 36 | .. | .. |
| PCI | | | | |
| No | 43 479/46 412 (93·7%) | 40 982/43 352 (94·5%) | 0·85 (0·48–1·51) | NA |
| Yes | 2933/46 412 (6·3%) | 2370/43 352 (5·5%) | .. | .. |
| NA | 9032 | 12 137 | .. | .. |
| CABG | | | | |
| No | 46 092/46 400 (99·3%) | 43 125/43 337 (99·5%) | 1·14 (0·75–1·73) | NA |
| Yes | 308/46 400 (0·7%) | 212/43 337 (0·5%) | .. | .. |
| NA | 9044 | 12 152 | .. | .. |

Data are n/N (%), n, or median (IQR), unless otherwise specified. Fixed-effect models were not estimated for secondary outcomes. CABG=coronary artery bypass grafting. MI=myocardial infarction. NA=not available. OR=odds ratio. PCI=percutaneous coronary intervention. *For the random-effects analyses, a two-stage meta-analysis was used for all primary outcomes and PCI, whereas a one-stage meta-analysis was used for all other secondary outcomes because of rare events. Fixed-effect analyses were post hoc. †The primary safety outcome was not assessed in 58 patients who died within 12 h (32 in the 0/3 h group and 26 in the 0/1 h group), because these deaths were considered index events rather than trial outcomes, and was unavailable for 14 patients without 30-day follow-up data (four in the 0/3 h group and ten in the 0/1 h group).

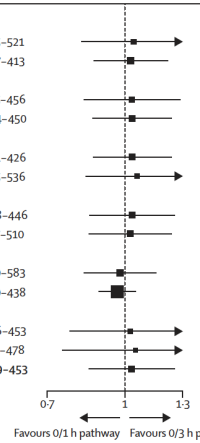
*Table 3*: Primary and secondary outcomes




(Figure 2 continues on next page)

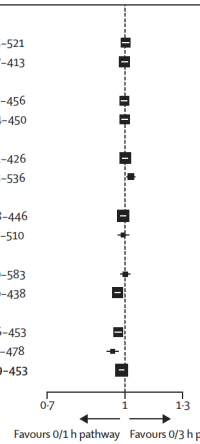
C

| | Number of patients/ total number of patients | 0/1 h pathway | | 0/3 h pathway | | OR (95% CI) |
|---|---|---|---|---|---|---|
| | | Median, min | IQR | Median, min | IQR | |
| **Age group, years (p=0·81)** | | | | | | |
| ≥65 | 21145/21282 | 359 | 240–554 | 347 | 235–521 | 1·04 (0·82–1·32) |
| <65 | 33 616/32 809 | 290 | 199–436 | 285 | 197–413 | 1·03 (0·87–1·21) |
| **Sex (p=0·82)** | | | | | | |
| Female | 26593/25874 | 320 | 217–485 | 313 | 215–456 | 1·03 (0·83–1·28) |
| Male | 28164/28216 | 308 | 207–476 | 303 | 204–450 | 1·03 (0·86–1·23) |
| **Diabetes (p=0·72)** | | | | | | |
| No | 39703/40726 | 294 | 201–447 | 295 | 201–426 | 1·03 (0·86–1·23) |
| Yes | 9365/10038 | 360 | 239–562 | 352 | 235–536 | 1·05 (0·83–1·33) |
| **Previous myocardial infarction (p=0·84)** | | | | | | |
| No | 49589/48051 | 312 | 210–475 | 305 | 208–446 | 1·03 (0·85–1·25) |
| Yes | 5172/6040 | 340 | 227–540 | 336 | 217–510 | 1·02 (0·85–1·24) |
| **GFR (p=0·87)** | | | | | | |
| <60 | 6972/6214 | 412 | 274–647 | 381 | 270–583 | 0·98 (0·83–1·15) |
| ≥60 | 35883/32990 | 312 | 213–471 | 305 | 210–438 | 0·96 (0·89–1·05) |
| **Ischaemia on ECG (p=0·23)** | | | | | | |
| No | 30915/34754 | 300 | 207–451 | 308 | 206–453 | 1·02 (0·78–1·35) |
| Yes | 4266/5248 | 279 | 162–446 | 303 | 171–478 | 1·05 (0·75–1·46) |
| **Overall** | **54761/54091** | **314** | **211–481** | **308** | **209–453** | **1·03 (0·85–1·25)** |




D

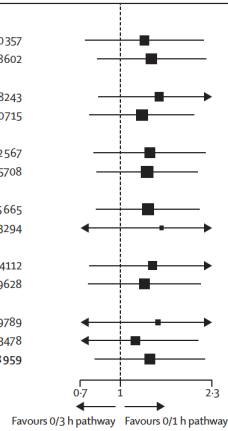
| | Number of patients/ total number of patients | 0/1 h pathway | | 0/3 h pathway | | OR (95% CI) |
|---|---|---|---|---|---|---|
| | | Median, min | IQR | Median, min | IQR | |
| **Age group, years (p=0·47)** | | | | | | |
| ≥65 | 21145/21282 | 359 | 240–554 | 347 | 235–521 | 1·01 (0·99–1·02) |
| <65 | 33616/32809 | 290 | 199–436 | 285 | 197–413 | 1·00 (0·99–1·02) |
| **Sex (p=0·49)** | | | | | | |
| Female | 26593/25874 | 320 | 217–485 | 313 | 215–456 | 1·00 (0·99–1·02) |
| Male | 28164/28216 | 308 | 207–476 | 303 | 204–450 | 1·00 (0·99–1·02) |
| **Diabetes (p=0·67)** | | | | | | |
| No | 39703/40726 | 294 | 201–447 | 295 | 201–426 | 1·00 (0·99–1·02) |
| Yes | 9365/10038 | 360 | 239–562 | 352 | 235–536 | 1·03 (1·01–1·05) |
| **Previous myocardial infarction (p=0·97)** | | | | | | |
| No | 49589/48051 | 312 | 210–475 | 305 | 208–446 | 0·99 (0·98–1·01) |
| Yes | 5172/6040 | 340 | 227–540 | 336 | 217–510 | 1·00 (0·97–1·02) |
| **GFR (p=0·12)** | | | | | | |
| <60 | 6972/6214 | 412 | 274–647 | 381 | 270–583 | 1·01 (0·98–1·03) |
| ≥60 | 35883/32990 | 312 | 213–471 | 305 | 210–438 | 0·97 (0·96–0·98) |
| **Ischaemia on ECG (p=0·00046)** | | | | | | |
| No | 30915/34754 | 300 | 207–451 | 308 | 206–453 | 0·97 (0·96–0·99) |
| Yes | 4266/5248 | 279 | 162–446 | 303 | 171–478 | 0·95 (0·92–0·97) |
| **Overall** | **54761/54091** | **314** | **211–481** | **308** | **209–453** | **0·99 (0·98–1·00)** |




(Figure 2 continues on next page)

E

| | 0/1 h pathway | | 0/3 h pathway | | OR (95% CI) |
|---|---|---|---|---|---|
| | Direct discharge | Not directly discharged | Direct discharge | Not directly discharged | |
| **Age group, years (p=0·68)** | | | | | |
| ≥65 | 11685 | 9785 | 11519 | 10357 | 1·25 (0·73–2·13) |
| <65 | 25505 | 8514 | 24966 | 8602 | 1·33 (0·81–2·18) |
| **Sex (p=0·12)** | | | | | |
| Female | 18588 | 8218 | 17971 | 8243 | 1·43 (0·82–2·48) |
| Male | 18599 | 10080 | 18514 | 10715 | 1·22 (0·76–1·96) |
| **Diabetes (p=0·93)** | | | | | |
| No | 28007 | 12154 | 28886 | 12567 | 1·31 (0·79–2·17) |
| Yes | 4602 | 5033 | 4956 | 5708 | 1·28 (0·81–2·03) |
| **Previous myocardial infarction (p=0·47)** | | | | | |
| No | 34311 | 15897 | 33361 | 15665 | 1·29 (0·81–2·05) |
| Yes | 2879 | 2402 | 3124 | 3294 | 1·46 (0·62–3·45) |
| **GFR (p=0·64)** | | | | | |
| <60 | 3202 | 4128 | 2840 | 4112 | 1·34 (0·76–2·38) |
| ≥60 | 25837 | 10404 | 23952 | 9628 | 1·25 (0·75–2·08) |
| **Ischaemia on ECG (p=0·48)** | | | | | |
| No | 23930 | 7556 | 25911 | 9789 | 1·41 (0·66–3·00) |
| Yes | 1811 | 2589 | 2132 | 3478 | 1·15 (0·65–2·03) |
| **Overall** | **37190** | **18299** | **36485** | **18959** | **1·31 (0·79–2·16)** |




F

| | 0/1 h pathway | | 0/3 h pathway | | OR (95% CI) |
|---|---|---|---|---|---|
| | Direct discharge | Not directly discharged | Direct discharge | Not directly discharged | |
| **Age group, years (p=0·41)** | | | | | |
| ≥65 | 11685 | 9785 | 11519 | 10357 | 1·08 (1·02–1·15) |
| <65 | 25505 | 8514 | 24966 | 8602 | 1·10 (1·04–1·16) |
| **Sex (p=0·034)** | | | | | |
| Female | 18588 | 8218 | 17971 | 8243 | 1·14 (1·08–1·21) |
| Male | 18599 | 10080 | 18514 | 10715 | 1·07 (1·01–1·13) |
| **Diabetes (p=0·93)** | | | | | |
| No | 28007 | 12154 | 28886 | 12567 | 1·11 (1·05–1·17) |
| Yes | 4602 | 5033 | 4956 | 5708 | 1·09 (1·01–1·18) |
| **Previous myocardial infarction (p=0·031)** | | | | | |
| No | 34311 | 15897 | 33361 | 15665 | 1·10 (1·05–1·16) |
| Yes | 2879 | 2402 | 3124 | 3294 | 1·16 (1·06–1·27) |
| **GFR (p=0·88)** | | | | | |
| <60 | 3202 | 4128 | 2840 | 4112 | 1·05 (0·96–1·15) |
| ≥60 | 25837 | 10404 | 23952 | 9628 | 1·07 (1·01–1·13) |
| **Ischaemia on ECG (p=0·014)** | | | | | |
| No | 23930 | 7556 | 25911 | 9789 | 1·19 (1·12–1·27) |
| Yes | 1811 | 2589 | 2132 | 3478 | 1·01 (0·92–1·12) |
| **Overall** | **37190** | **18299** | **36485** | **18959** | **1·11 (1·06–1·17)** |

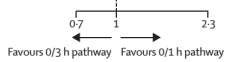



***Figure 2:*** **Forest plots of two-stage subgroup analyses for the primary outcomes using random-effects and post-hoc fixed-effect models**
(A) All-cause death or new type 1 myocardial infarction within 30 days, random-effects model. (B) All-cause death or new type 1 myocardial infarction within 30 days, post-hoc fixed-effect model. (C) Median emergency department length of stay in min, random-effects model. (D) Median emergency department length of stay in min, post-hoc fixed-effect model. (E) Direct discharge from the emergency department, random-effects model. (F) Direct discharge from the emergency department, post-hoc fixed-effect model. p values are for interaction. Estimated GFR is in mL/min per 1·73 $m^2$. ECG=electrocardiogram. GFR=glomerular filtration rate. OR=odds ratio.

**Added value of this study**

To our knowledge, this is the first systematic review and individual participant data meta-analysis of the randomised evidence evaluating the safety and efficacy of the 0/1 h pathway across different countries and health-care systems. This study enabled harmonisation of clinically relevant outcomes that were defined or reported inconsistently across the individual trials. It provided harmonised estimates for all-cause death or new type 1 myocardial infarction within 30 days and reported emergency department length of stay and direct discharge from the emergency departments for the whole analysis population within each trial and across all included trials. This study further assessed heterogeneity across the included health-care settings and explored treatment effects in prespecified clinically relevant subgroups.

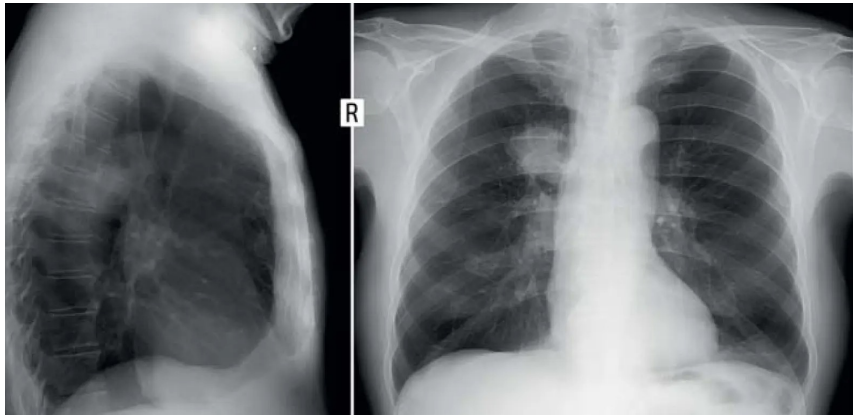
**Implications of all the available evidence**

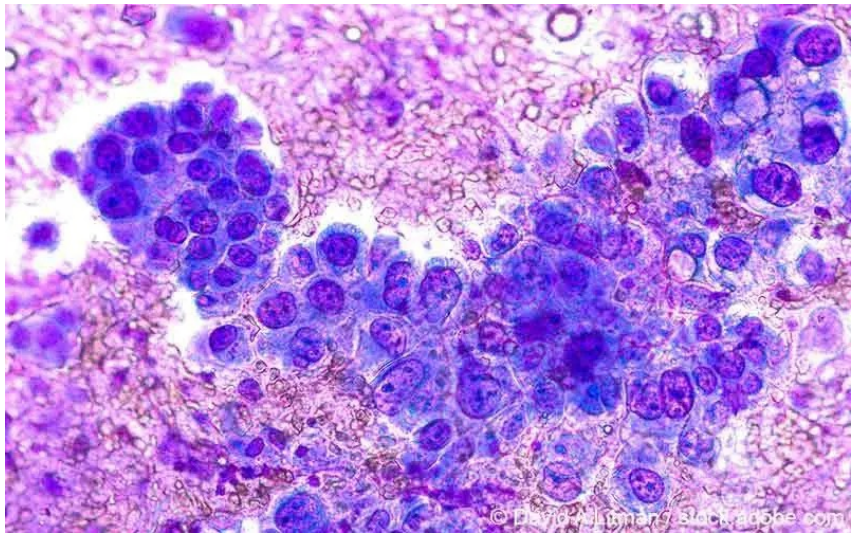
The provided evidence for the safety and efficacy of the 0/1 h pathway is complementary to that provided by each individual randomised trial. Across the included randomised trials, short-term adverse event rates were low with both pathways, but the pooled safety estimate remained imprecise. On average, earlier cardiac troponin retesting did not reduce emergency department length of stay or clearly increase direct discharge from the emergency department. Taken together, these findings suggest that shortening the cardiac troponin sampling interval alone should not be expected to produce uniform improvements in emergency department length of stay or direct discharge across health-care systems.

Das **nicht-kleinzellige Lungenkarzinom** (NSCLC, von englisch *non-small cell lung cancer*) ist mit rund 85 % aller Fälle die häufigste Form von Lungenkrebs.

**Häufigste Subtypen**

- **Adenokarzinom:** Häufigster Subtyp (ca. 40–50 %), wächst meist in den äußeren Bereichen der Lunge und tritt verhältnismäßig oft auch bei Nichtrauchern auf.
- **Plattenepithelkarzinom:** Entsteht meist in den größeren Atemwegen (zentral), ist stark mit dem Rauchen verbunden und betrifft häufiger Männer.
- **Großzelliges Karzinom:** Seltenerer Subtyp mit raschem Wachstum



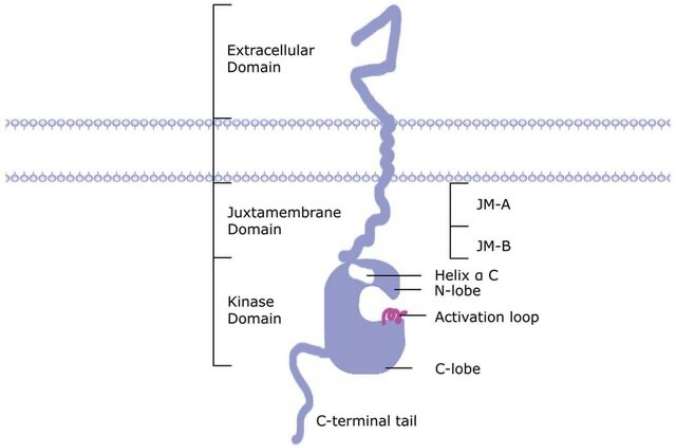
Der **HER3-Rezeptor** (Human Epidermal Growth Factor Receptor 3, kodiert durch das *ERBB3*-Gen) gehört zur Familie der HER-Rezeptortyrosinkinasen (neben HER1/EGFR, HER2 und HER4).

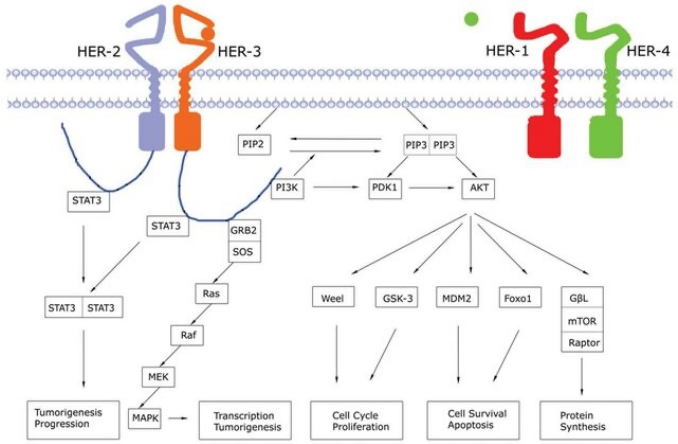
- **Erhöhte Aktivität durch Partnerschaft:** HER3 besitzt von Natur aus nur eine sehr schwache eigene Tyrosinkinase-Aktivität. Um Signale weiterzuleiten, verbindet er sich bevorzugt mit anderen Rezeptoren der Familie – insbesondere mit **HER2**.

- **Wachstum und Überleben:** Dieses HER2-HER3-Heterodimer bildet ein sehr starkes Signalnetzwerk (über den PI3K/Akt-Weg), das das Wachstum, die Teilung und das Überleben von Zellen steuert.

- **Rolle bei Krebserkrankungen:** HER3 ist in vielen soliden Tumoren (z. B. Brust-, Lungen-, Dickdarm-, Eierstock- und Bauchspeicheldrüsenkrebs) überexprimiert. Bei Brustkrebs findet man ihn bei rund 30 bis 50 % aller Mammakarzinome.

- **Therapieresistenz:** HER3 kann alternative Signalwege aktivieren, wodurch Krebszellen Resistenzen gegen Chemotherapien sowie gegen HER2- oder EGFR-gerichtete Medikamente entwickeln.



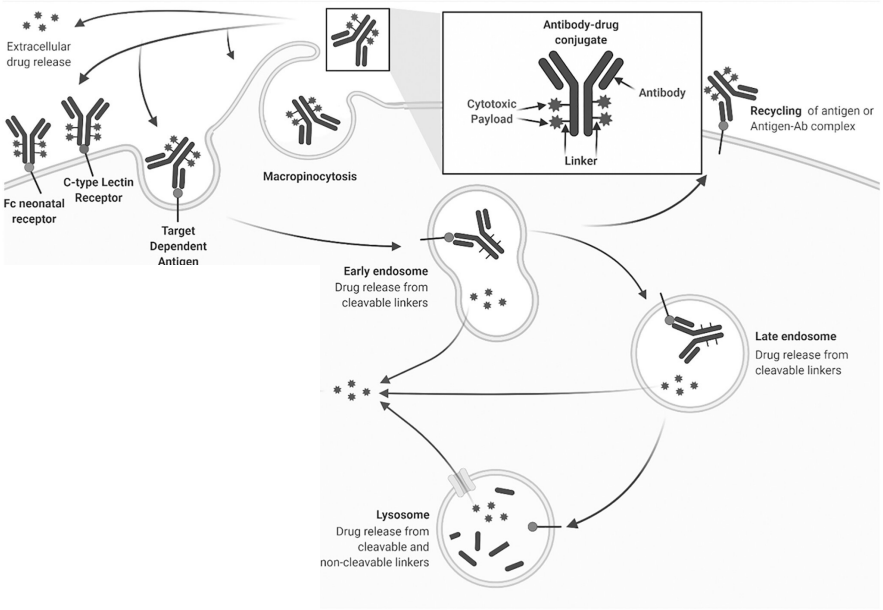



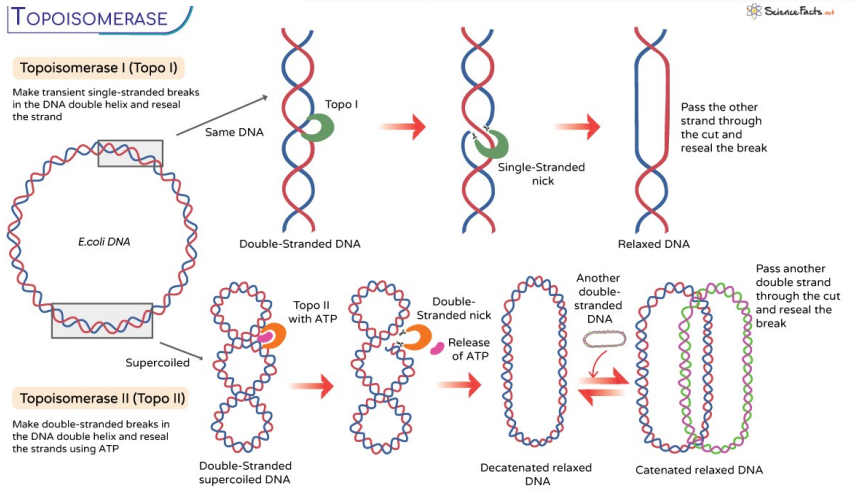
**Ruzaltatug Rezetecan** ist ein neuartiges Antikörper-Wirkstoff-Konjugat (Antibody-Drug Conjugate, ADC), das gezielt für die Behandlung von fortgeschrittenem, EGFR-mutiertem nicht-kleinzelligem Lungenkrebs (NSCLC) entwickelt wird.

## Wirkmechanismus

Das Medikament funktioniert nach dem Prinzip einer "zielgerichteten Chemotherapie":

- **Zielstruktur (Target):** Es richtet sich gegen das Protein **HER3** (Human Epidermal Growth Factor Receptor 3). Dieses Protein wird von Tumorzellen oft vermehrt gebildet, insbesondere wenn sie eine Resistenz gegen herkömmliche EGFR-Inhibitoren (wie Osimertinib) entwickelt haben.
- **Wirkstoff (Payload):** Der Antikörper ist an **Rezetecan** gekoppelt, einen starken Topoisomerase-I-Inhibitor. Sobald das ADC an die Krebszelle bindet und in sie eindringt, wird der Wirkstoff freigesetzt, blockiert die Zellteilung und führt zum Absterben der Tumorzelle.



Anti-HER3 coupled with TI inhibitor

# Ruzaltatug rezetecan versus chemotherapy for *EGFR*-mutated advanced non-small-cell lung cancer progressing after EGFR tyrosine kinase inhibitor therapy (HERON-Lung01): interim analysis of a randomised, open-label, phase 3 trial in China


## Summary

**Background** Ruzaltatug rezetecan is a novel HER3-directed antibody–drug conjugate that has shown promising antitumour activity and manageable safety in pretreated *EGFR*-mutated non-small-cell lung cancer (NSCLC) in a phase 1 trial. We aimed to compare the efficacy and safety of ruzaltatug rezetecan with chemotherapy in patients with *EGFR*-mutated advanced NSCLC that had progressed after EGFR tyrosine kinase inhibitor (TKI) therapy.

**Methods** HERON-Lung01 is a randomised, open-label, phase 3 trial conducted at 62 sites in China. Eligible patients were aged 18–75 years, with locally advanced or metastatic non-squamous NSCLC harbouring an *EGFR* activating mutation (exon 19 deletion or L858R mutation), and had progressed during or after EGFR-TKI therapy. Patients were randomly assigned (1:1) to receive ruzaltatug rezetecan 8·0 mg/kg or chemotherapy comprising pemetrexed 500 mg/m² plus carboplatin (area under the curve 5) or cisplatin 75 mg/m² for four cycles, followed by maintenance pemetrexed. All treatments were administered intravenously on day 1 of each 3-week cycle. Block randomisation was stratified by presence of brain metastases, *EGFR* mutation subtype, and use of a first-line third-generation EGFR-TKI. The primary endpoint was progression-free survival (PFS), as assessed by blinded independent central review (BICR), in the intention-to-treat population. This trial is registered with ClinicalTrials.gov (NCT06671379). Recruitment is complete, with the trial ongoing.

**Findings** Between Nov 29, 2024, and Jan 29, 2026, 498 patients were randomly assigned to receive ruzaltatug rezetecan (n=250) or chemotherapy (n=248). The median age was 60·0 years (IQR 54·0–68·0); 276 (55%) patients were female and 222 (45%) male. At the prespecified interim PFS analysis, median follow-up was 7·7 months (95% CI 7·1–8·3). BICR-assessed PFS was significantly longer with ruzaltatug rezetecan than with chemotherapy (median 8·3 months *vs* 5·4 months; hazard ratio 0·47 [95% CI 0·36–0·60]; one-sided p<0·0001). Grade 3 or worse treatment-related adverse events (TRAEs) occurred in 101 (41%) of 248 patients receiving ruzaltatug rezetecan and 93 (39%) of 239 patients receiving chemotherapy, most commonly decreased neutrophil count (64 [26%] of 248 patients *vs* 46 [19%] of 239 patients), decreased white blood cell count (29 [12%] *vs* 29 [12%]), and anaemia (15 [6%] *vs* 26 [11%]). TRAEs led to treatment discontinuation in three (1%) patients in the ruzaltatug rezetecan group and three (1%) in the chemotherapy group. One death (unknown cause) in the ruzaltatug rezetecan group was considered by the investigator to be possibly treatment related.

**Interpretation** Ruzaltatug rezetecan significantly prolonged PFS compared with chemotherapy, with a manageable safety profile, in EGFR-TKI-resistant, *EGFR*-mutated advanced NSCLC. These data support ruzaltatug rezetecan as a potential treatment option in this setting.

**Funding** Jiangsu Hengrui Pharmaceuticals.

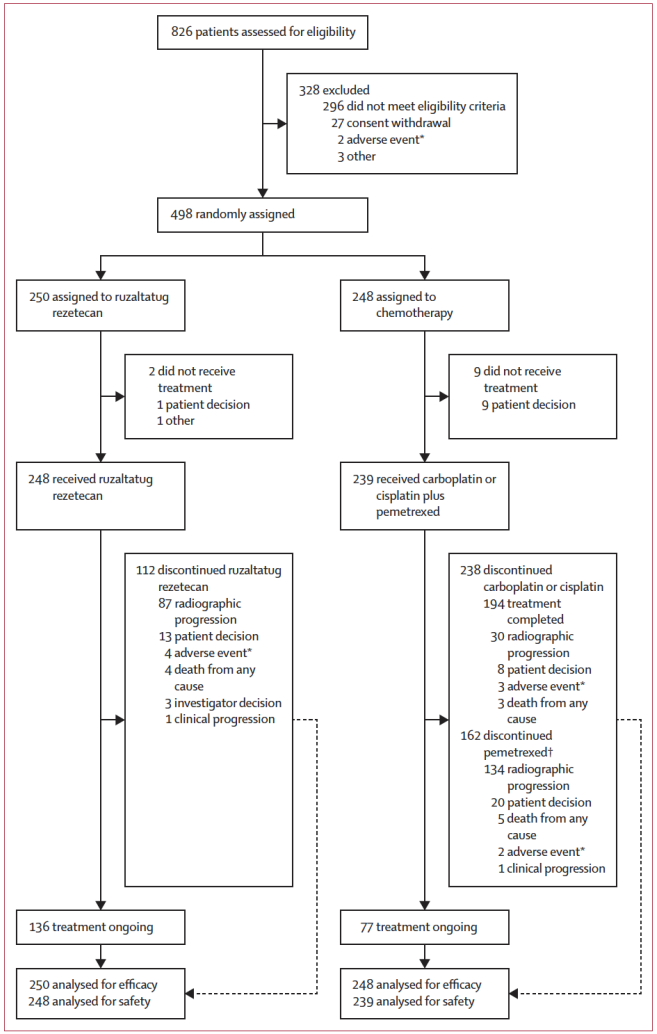



***Figure 1:*** **Trial profile**
*Includes adverse events from any cause; three events in the ruzaltatug rezetecan group were treatment related. †Among the 162 patients who discontinued all allocated study treatments in the chemotherapy group, 48 crossed over to receive ruzaltatug rezetecan.

| | Ruzaltatug rezetecan (n=250) | Chemotherapy (n=248) |
|---|---|---|
| Median age (IQR), years | 60 (54–67) | 61 (55–68) |
| Sex | | |
| Male | 116 (46%) | 106 (43%) |
| Female | 134 (54%) | 142 (57%) |
| Asian race | 250 (100%) | 248 (100%) |
| Smoking history | | |
| Current or former smoker | 70 (28%) | 80 (32%) |
| Never smoked | 180 (72%) | 168 (68%) |
| ECOG performance status score | | |
| 0 | 57 (23%) | 56 (23%) |
| 1 | 192 (77%) | 192 (77%) |
| Unknown* | 1 (<1%) | 0 |
| Adenocarcinoma | 250 (100%) | 248 (100%) |
| Disease stage | | |
| IIIB or IIIC | 5 (2%) | 7 (3%) |
| IV | 245 (98%) | 241 (97%) |
| Brain metastases | 48 (19%) | 47 (19%) |
| Liver metastases | 35 (14%) | 35 (14%) |
| *EGFR* mutation subtype† | | |
| Exon 19 deletion | 154 (62%) | 152 (61%) |
| L858R mutation | 96 (38%) | 96 (39%) |
| Other | 53 (21%) | 46 (19%) |
| T790M mutation | 21 (8%) | 19 (8%) |
| Previous third-generation EGFR-TKI | 246 (98%) | 239 (96%) |
| First-line therapy | 194 (78%) | 194 (78%) |
| Previous antiangiogenic therapy | 23 (9%) | 26 (10%) |

Data are n (%) unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. TKI=tyrosine kinase inhibitor. *One patient who was ineligible on screening was inadvertently randomised; ECOG performance status was not assessed. †*EGFR* mutation status was assessed using tissue or blood samples. Other mutations refer to *EGFR* mutations co-occurring with L858R mutation or exon 19 deletion.

***Table 1:*** **Demographics and disease characteristics at baseline (intention-to-treat population)**

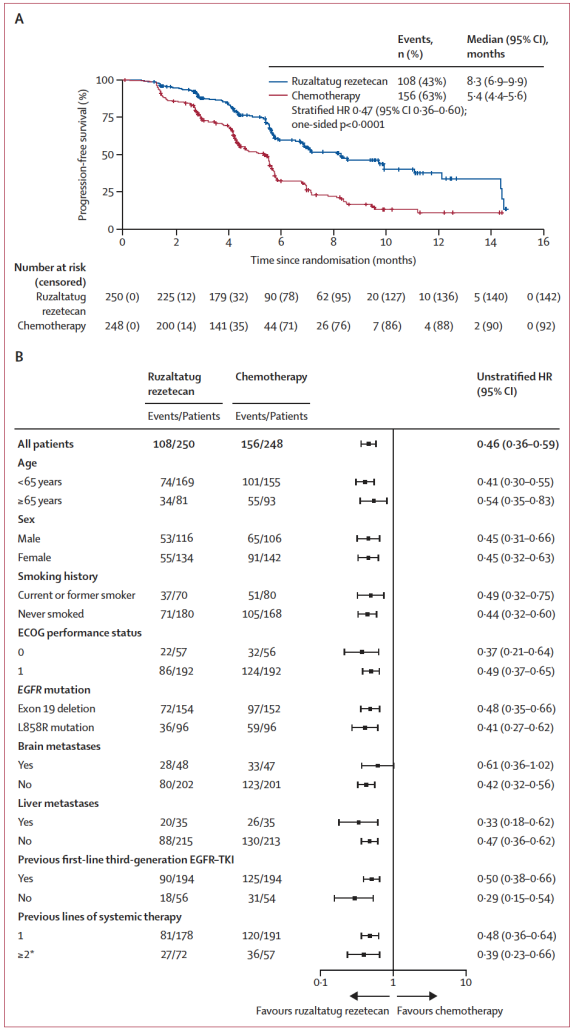



*Figure 2:* **Interim analysis of progression-free survival by blinded independent central review (intention-to-treat population)**
(A) Kaplan–Meier estimates for the interim analysis of progression-free survival. (B) Forest plot of progression-free survival in prespecified subgroups. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. TKI=tyrosine kinase inhibitor. *Patients with two or more previous lines of systemic therapy had sequential EGFR-TKI treatment.

| | Ruzaltatug rezetecan (n=250) | Chemotherapy (n=248) | Difference (95% CI)* |
|---|---|---|---|
| Best overall response, n (%) | | | |
| Complete response | 1 (<1%) | 0 | .. |
| Partial response | 149 (60%) | 85 (34%) | .. |
| Stable disease | 82 (33%) | 121 (49%) | .. |
| Progressive disease | 12 (5%) | 30 (12%) | .. |
| Not evaluable | 6 (2%) | 12 (5%) | .. |
| Objective response rate (95% CI) | 60·0% (53·8–65·9) | 34·3% (28·6–40·4) | 25·7 (17·0–33·9) |
| Disease control rate (95% CI) | 92·8% (88·9–95·4) | 83·1% (77·9–87·2) | 9·7 (4·0–15·5) |
| Median response duration, months (95% CI) | 8·5 (5·6–13·1) | 4·4 (4·2–5·8) | .. |
| Duration of response rate at 6 months (95% CI) | 56·0% (45·2–65·6) | 35·1% (21·7–48·8) | .. |
| Median time to first response (IQR), months | 1·5 (1·4–2·8) | 1·5 (1·4–2·8) | .. |

*Differences are expressed in percentage points.

***Table 2:* Tumour response by blinded independent central review (intention-to-treat population)**

| | Ruzaltatug rezetecan (n=248) | | Chemotherapy (n=239) | |
|---|---|---|---|---|
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any treatment-related adverse event | 247 (>99%) | 101 (41%) | 236 (99%) | 93 (39%) |
| Leading to dose reduction | 36 (15%) | .. | 24 (10%) | .. |
| Leading to dose interruption | 77 (31%) | .. | 66 (28%) | .. |
| Leading to treatment discontinuation | 3 (1%) | .. | 3 (1%) | .. |
| Leading to death* | 1 (<1%) | .. | 0 | .. |
| Serious | 38 (15%) | .. | 36 (15%) | .. |
| Treatment-related adverse events occurring in ≥10% in either group | | | | |
| Neutrophil count decreased | 177 (71%) | 64 (26%) | 135 (56%) | 46 (19%) |
| White blood cell count decreased | 157 (63%) | 29 (12%) | 144 (60%) | 29 (12%) |
| Anaemia | 151 (61%) | 15 (6%) | 183 (77%) | 26 (11%) |
| Alopecia | 148 (60%) | 0 | 30 (13%) | 0 |
| Nausea | 137 (55%) | 4 (2%) | 93 (39%) | 5 (2%) |
| Decreased appetite | 135 (54%) | 3 (1%) | 95 (40%) | 0 |
| Asthenia | 98 (40%) | 8 (3%) | 78 (33%) | 2 (1%) |
| Alanine aminotransferase increased | 94 (38%) | 2 (1%) | 93 (39%) | 0 |
| Aspartate aminotransferase increased | 84 (34%) | 3 (1%) | 91 (38%) | 0 |
| Gamma-glutamyltransferase increased | 64 (26%) | 5 (2%) | 44 (18%) | 5 (2%) |
| Constipation | 63 (25%) | 0 | 59 (25%) | 0 |
| Platelet count decreased | 57 (23%) | 5 (2%) | 98 (41%) | 22 (9%) |
| Hypoalbuminaemia | 53 (21%) | 0 | 33 (14%) | 0 |
| Vomiting | 52 (21%) | 3 (1%) | 41 (17%) | 5 (2%) |
| Lymphocyte count decreased | 48 (19%) | 6 (2%) | 38 (16%) | 12 (5%) |
| Fatigue | 47 (19%) | 2 (1%) | 36 (15%) | 0 |
| Weight decreased | 43 (17%) | 1 (<1%) | 30 (13%) | 0 |
| Blood alkaline phosphatase increased | 43 (17%) | 0 | 24 (10%) | 0 |
| Dizziness | 36 (15%) | 1 (<1%) | 20 (8%) | 0 |
| Blood lactate dehydrogenase increased | 30 (12%) | 0 | 24 (10%) | 0 |

Data are n (%). Post-crossover adverse events were excluded from the analyses. *One death of unknown cause was reported in the ruzaltatug rezetecan group.

***Table 3*: Treatment-related adverse events (safety population)**

**Implications of all the available evidence**

Our findings validate HER3 as a relevant therapeutic target in EGFR-TKI-resistant *EGFR*-mutated NSCLC. Ruzaltatug rezetecan significantly prolonged PFS with manageable safety, supporting it as a possible treatment option in this setting. Its differentiated safety and administration profile might distinguish ruzaltatug rezetecan from other available post-EGFR-TKI regimens, while its satisfactory tolerability provides a rationale for development in combination strategies. A phase 3 trial evaluating ruzaltatug rezetecan plus the third-generation EGFR-TKI aumolertinib as first-line treatment for *EGFR*-mutated advanced NSCLC is underway (NCT07183189).

# The 2026 report of the *Lancet* Countdown on health and climate change: a decade of escalating health harms and a decisive moment for all


## Executive Summary

The *Lancet* Countdown was established 10 years ago in 2016—the year the Paris Agreement entered into force—to annually assess the effects of climate change on health, and the health benefits of climate change interventions. Although insufficient to meet its goals, action since then has reduced projected greenhouse gas emissions, lowering end-of-21st-century expected temperature increase from 3·0–3·5°C to 2·6–3·4°C. The growth of zero-emission energy has exceeded expectations, delivering health and economic benefits globally. In parallel, recognition of the links between health and climate change has increased substantially (indicators 5.1–5.6), and tackling climate change has become a priority for global health, with WHO identifying it as the first strategic objective in its Fourteenth General Programme of Work.

Despite this progress, greenhouse gas emissions continue to reach record highs, climate change is increasingly affecting health and threatening people's survival worldwide, and the window of opportunity to avoid a potentially catastrophic future is rapidly closing. Weakening multilateralism and growing climate change disinformation, denialism, and scepticism are now increasingly undermining collective action and threatening to reverse progress to date. Yet, this moment of disruption also presents an opportunity. The system-wide reform of the UN, under the UN80 initiative, and the impending reform of the Global Health Architecture, provide opportunities to strengthen cross-sectoral coordination, optimise resources, and enable an effective global response to climate change for a healthier future.


Not much change in climate-change trends

### *Panel 1*: Global enablers to change course towards a safer future

Decades of unmet commitments mean that avoiding the most catastrophic outcomes of climate change now requires a new approach to deliver system-wide change at a scale and pace matching the immediacy and gravity of the hazards otherwise faced.[49] Such response requires actions across sectors, spanning mitigation, adaptation, loss and damage, and finance. To enable such response, the evidence in this report informs the following recommendations at the global level:

**(1) Recognise, prepare for, and respond to the health emergencies of climate change through established WHO and broader UN mechanisms, and develop a new WHO instrument to formally recognise and address climate change as a global health emergency**

Utilise the WHO Emergency Response Framework, the International Health Regulations, and the Inter-Agency Standing Committee instruments to recognise, prevent, prepare for, and respond to the health and broader impacts of health emergencies driven by climate change, including by grading climate change-related emergency events and coordinating a cross-sectoral response that aligns surveillance and early warning systems with anticipatory action, health system preparedness, and rapid and effective response that safeguards health systems and resource mobilisation. Additionally, respond to the scientific evidence, including within this report, demonstrating that climate change is increasingly fuelling health emergencies, and that addressing their root cause requires coordinated, multisectoral and international mitigation and adaptation actions. Establish a new WHO instrument to formally recognise and address climate change as a global health emergency with multiple linked impacts, enabling a coordinated international response that enables sustained anticipatory and preventative action, cross-sectoral and coordinated emergency management, and sustained resource mobilisation.

**(2) Align global governance and international systems around climate change and health as a top priority and optimise the deployment of international resources to address it**

Addressing climate change-related health risks requires coordinated and urgent adaptation and mitigation responses across sectors. Countries have the opportunity to build on the UN80 Initiative and the upcoming post-2030 agenda to deliver a new international governance architecture that enables and prioritises a coordinated, cross-sectoral, international response to climate change and health, thereby optimising the use of resources, maximising cost savings, breaking down silos, and ensuring that interventions deliver mutually reinforcing benefits across all sectors.

**(3) Prioritise and promote the urgent, just, and equitable reduction of greenhouse gas emissions as a global health imperative**

Develop global and national roadmaps to deliver a just and healthy reduction of greenhouse gas emissions, including through a just transition away from polluting fuels (biomass and fossil fuels). Ensure these roadmaps account for, quantify, and maximise the health benefits from reduced air pollution; improved access to safe, reliable, and affordable energy; healthier diets; improved equity; and more active lifestyles, while avoiding the health harms from extractive industries and over-reliance on technologies which perpetuate the use of fossil fuels or introduce new health harms. Engage health professionals and organisations in the design and implementation of these roadmaps.

**(4) Put health at the centre of climate action by placing present and future mortality reduction, health and wellbeing as core objectives and key measures of success across all climate action**

Integrating health outcomes into the target-setting, monitoring, and evaluation of climate change interventions across UN programmes, the post-2030 agenda, and national policies including climate finance allocation, and the planning, monitoring, and implementation of climate action across sectors. This will help ensure that climate policies deliver and maximise their potential benefits for people and the planet on which their health depends, while identifying and avoiding unintended health harms from the transition.

**(5) Establish a global climate change and health data commons as critical public infrastructure and a global public good**

The commons would improve the availability, interoperability, and integration of climate and health data disaggregated by relevant population groups and at high temporal and geographical resolution. This would support the development of climate change and health surveillance and health early warning systems; facilitate knowledge sharing to strengthen countries' capacity to collect, manage, and share data; and help bridge critical data gaps. By providing a shared evidence base, the commons would strengthen the ability of countries to develop cohesive, effective, and evidence-informed responses that protect health from the impacts of climate change.

**(6) Increase the provision of grant-based and highly concessional finance for climate change and health interventions, including by meeting international obligations**

Meet international interventions and obligations, including Article 9.1 of the Paris Agreement and the International Court of Justice Advisory Opinion on the Obligations of States in Respect of Climate Change to support equitable climate action that protects and promotes health. Such finance is needed at a scale sufficient to enable implementation of adaptation and mitigation actions without exacerbating debt burdens through additional borrowing and interest repayments. Strengthening the availability of accessible, predictable, and equitable finance is essential to addressing the shared risks of climate change, reducing global inequities, and protecting the health and wellbeing of people in all countries.

### *Panel 2*: The 2026 report of the *Lancet* Countdown on health and climate change indicators

**Health hazards, exposures, and impacts**

*1.1: heat and health*
- 1.1.1: exposure of vulnerable populations to heatwaves
- 1.1.2: heat and physical activity
- 1.1.3: change in labour capacity
- 1.1.4: rising night-time temperatures and sleep loss
- 1.1.5: heat-related mortality

*1.2: health and extreme weather-related events*
- 1.2.1: wildfires
- 1.2.2: drought
- 1.2.3: extreme precipitation
- 1.2.4: air pollution from sand and dust storms

*1.3: climate suitability for infectious disease transmission*
- 1.3.1: vector-borne diseases
- 1.3.2: water-borne diseases

*1.4: food insecurity and undernutrition*

**Adaptation, planning, and resilience for health**

*2.1: assessment and planning of health adaptation*
- 2.1.1: national assessments of climate change vulnerability and adaptation for health
- 2.1.2: National Adaptation Plans for health
- 2.1.3: city-level or state-level climate change risk assessments

*2.2: enabling conditions, adaptation delivery, and implementation*
- 2.2.1: climate information for health
- 2.2.2: benefits and harms of air conditioning
- 2.2.3: urban green and blue spaces
- 2.2.4: detection of, preparedness for, and response to health emergencies
- 2.2.5: climate and health education and training

*2.3: vulnerabilities, health risk, and resilience to climate change*
- 2.3.1: vulnerability to severe mosquito-borne disease
- 2.3.2: lethality of extreme weather events
- 2.3.3: climate change, migration, and displacement

**Mitigation actions and health co-benefits**

*3.1: energy use, energy generation, and health*
- 3.1.1: energy systems and health
- 3.1.2: household energy use
- 3.1.3: sustainable and healthy road transport

*3.2: air quality and health co-benefits*
- 3.2.1: mortality from ambient air pollution by sector
- 3.2.2: household air pollution
- 3.2.3: air pollution and health impacts driven by international trade

*3.3: food, agriculture, and health co-benefits*
- 3.3.1: emissions from agricultural production and consumption
- 3.3.2: diet and health co-benefits

*3.4: tree cover loss*

*3.5: health sector emissions*
- 3.5.1: health-care sector emissions and damages
- 3.5.2: health-care greenhouse gas footprinting efforts

**Economics and finance**

*4.1: the economic impact of climate change and its mitigation*
- 4.1.1: economic losses due to weather-related extreme events
- 4.1.2: costs of heat-related mortality
- 4.1.3: loss of earnings from heat-related labour capacity reduction
- 4.1.4: costs of the health impacts of air pollution

*4.2: the transition to net zero-carbon, health-supporting economies*
- 4.2.1: employment in low-carbon and high-carbon industries
- 4.2.2: compatibility of fossil fuel company strategies with the Paris Agreement
- 4.2.3: stranded coal assets from the energy transition
- 4.2.4: country preparedness for the transition to net zero

*4.3: financial transitions for a healthy future*
- 4.3.1: clean energy investment
- 4.3.2: net value of fossil fuel subsidies and carbon prices
- 4.3.3: health adaptation finance flows and disclosed needs
- 4.3.4: health research funding

**Public and political engagement with health and climate change**

*5.1: media engagement*

*5.2: individual engagement*

*5.3: scientific engagement*
- 5.3.1: scientific articles on health and climate change
- 5.3.2: scientific engagement on the health impacts of climate change

*5.4: political engagement*
- 5.4.1: government engagement
- 5.4.2: engagement by international organisations

*5.5: legislative engagement*

*5.6: corporate-sector engagement*

# Generalised eruptive histiocytosis mimicking lymphoma relapse in a patient with previous diffuse large B-cell lymphoma

A 92-year-old man with a history of diffuse large B-cell lymphoma treated with chemoradiotherapy, and later with radiotherapy for an isolated cutaneous relapse with complete response, presented with a 1-month history of multiple asymptomatic erythematous-to-violaceous papules and nodules on the face, trunk, and upper limbs. Given his oncological history and previous skin involvement, lymphoma relapse was the leading diagnostic concern, with cutaneous metastases and sarcoidosis also considered. However, skin biopsies showed a non-Langerhans cell histiocytic infiltrate expressing CD45, CD68, and CD163, without CD1a, CD20, PAX5, S100, or Langerin expression. Skin and blood flow cytometry identified no abnormal cell populations, and a PET-CT scan showed no abnormal metabolic activity. Clinicopathological correlation narrowed the differential to group C (cutaneous) histiocytosis, and subsequent spontaneous regression of the lesions over 3 months without treatment supported the diagnosis of generalised eruptive histiocytosis. At 15 months of follow-up, there was no recurrence or evidence of active disease. This case illustrates that cutaneous histiocytoses can mimic several inflammatory and neoplastic conditions, including lymphoma relapse, reinforcing the need to actively resist cognitive bias in people who have had cancer through reflective reassessment, broad differential diagnosis, and biopsy confirmation.

Als **Histiozytosen** bezeichnet man eine heterogene Gruppe seltener Erkrankungen, bei denen es zu einer krankhaften Vermehrung (Proliferation) und Ansammlung von Histiozyten – also von Abwehrzellen wie Makrophagen (Fresszellen), Monozyten oder dendritischen Zellen – im Gewebe kommt.



*Figure 1:* **Clinical presentation**
Numerous painless erythematous-to-violaceous papules and nodules involving the face, trunk, and upper limbs at presentation. Close-up view of truncal lesions, which were firm, rubbery, and fixed on palpation.

- **L-Gruppe (Langerhans-Gruppe):** Umfasst Erkrankungen wie die **Langerhanszell-Histiozytose (LCH)**, die am häufigsten im Kindesalter auftritt und Knochen, Haut oder Organe betreffen kann, sowie die seltene Erdheim-Chester-Erkrankung (ECD).
- **C-Gruppe (Kutane Gruppe):** Umfasst gutartige und reaktive Formen, die vor allem die Haut betreffen (z. B. das juvenile Xanthogranulom).
- **R-Gruppe (Rosai-Dorfman-Gruppe):** Bezeichnet die Rosai-Dorfman-Destombes-Erkrankung (RDD), die oft durch geschwollene Lymphknoten und Hautknötchen auffällt.

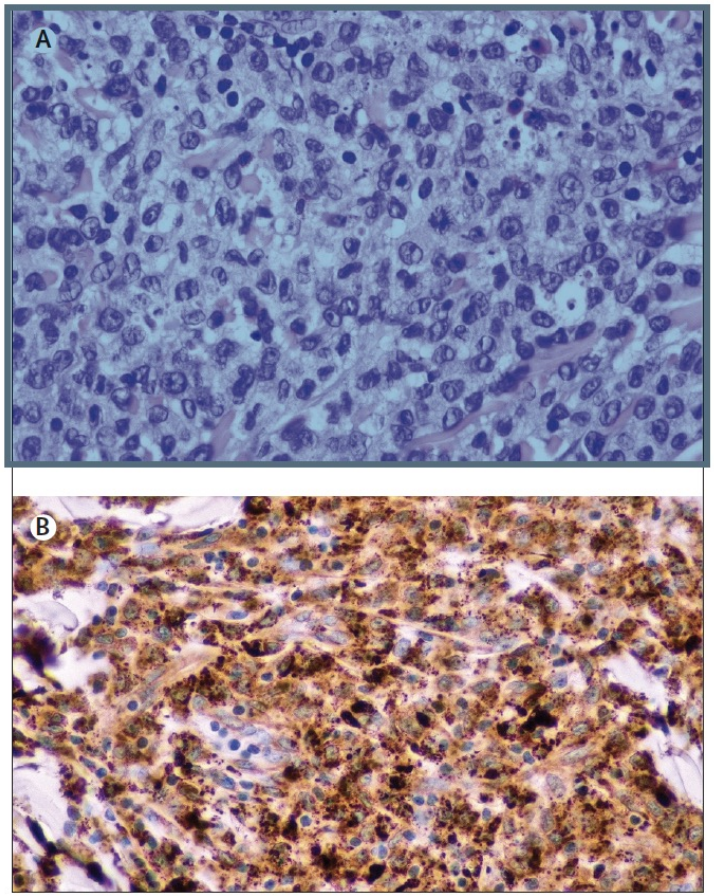



*Figure 2:* **Histopathological findings**
(A) Dense dermal infiltrate composed of large cells with pale cytoplasm and vesicular nuclei (haematoxylin and eosin; ×400 magnification).
(B) Immunohistochemical staining showing strong CD68 expression in lesional cells (×400 magnification).

| | Group L | Group R | Group C | | |
|---|---|---|---|---|---|
| | Langerhans cell histiocytosis | Rosai–Dorfman disease | Xanthoma disseminatum | Progressive nodular histiocytosis | Generalised eruptive histiocytosis |
| Epidemiology | Children more commonly than adults; can occur at any age | Young adults (mean age at diagnosis ~20 years); predominantly occurs in males | Young adults; predominantly occurs in males | Middle-aged adults (median age at diagnosis ~50 years); no sex-based difference in occurence | Adults more commonly than children; predominantly occurs in males |
| Clinical findings | Single-system or multisystem disease, often involving bone, skin, pituitary, or lung; in adults, disease can follow an indolent course | Classically massive cervical lymphadenopathy; can involve nasal cavity, lung, and bone | Hundreds of symmetrical orange to yellow-brown papules and nodules; often involves eyelids, skin folds, and mucosae | Multiple pink to brown lesions up to 5 cm; frequent mucosal involvement | Innumerable reddish papules, mainly on trunk and proximal limbs; usually spares skin folds and mucosae |
| Histological findings | Dermal infiltrate of large histiocytes with grooved reniform nuclei, typically with epidermotropism | Dense dermal infiltrate of large pale histiocytes with vesicular nuclei and variable emperipolesis, combined with plasma cells | Dermal infiltrate of histiocytes, foam cells, spindle cells, and Touton giant cells, often with scalloped histiocytes | Dermal infiltrate of histiocytes, foam cells, and spindle cells, often in a storiform pattern within a delicate fibrocollagenous stroma | Superficial to mid-dermal infiltrate of pale histiocytes, often spindle-shaped, usually lacking foam cells and giant cells |
| Immunophenotype | CD1a+, CD207+, S100+ | CD1a–, S100+, CD207– | CD1a–, S100–, CD207– | CD1a–, S100–, CD207– | CD1a–, S100–, CD207– |
| *BRAF* mutations | Common | Rare | Rare | Rare | Rare |
| Reported associations with malignancy | Lymphoma, leukaemia, and myelodysplastic syndrome | No consistent association established | Waldenström macroglobulinaemia | Acute and chronic myeloid leukaemia | Acute leukaemia; other myeloid neoplasms |
| Evolution | Variable; depends on the extent and site of organ involvement | Variable; depends on the extent and site of organ involvement | Slow involution over years or progression | Progressive | Most often spontaneous involution; rarely evolves into other non-Langerhans histiocytosis |

Adapted from Emile and colleagues[4] and Patterson.[5]

***Table:*** **Distinguishing features of the histiocytoses considered in the differential diagnosis**



***Figure 3:*** **Clinical course**
Spontaneous resolution of cutaneous lesions 3 months after presentation. Close-up view of the trunk showing no residual scarring and only minimal post-inflammatory hyperpigmentation.

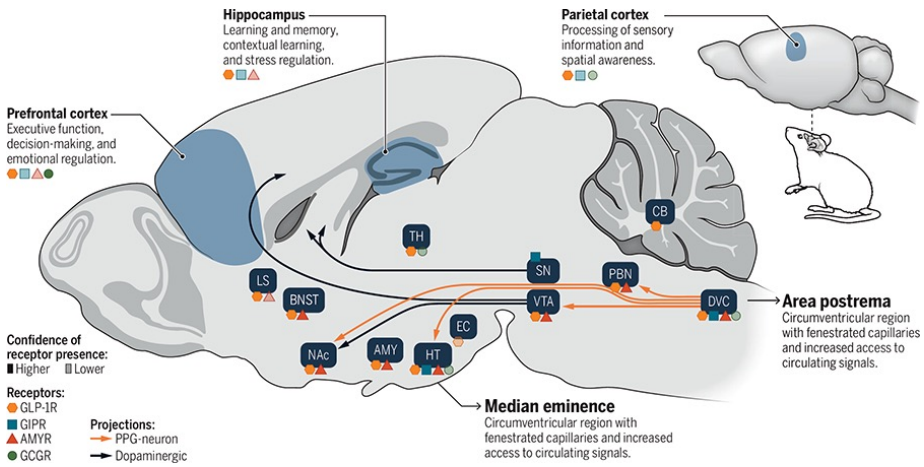
### *Panel:* Learning points

- Cutaneous histiocytoses have a broad clinical spectrum and can mimic malignant or inflammatory disease, making integrated clinical, histological, and immunophenotypic assessment essential.
- In people who have had cancer new lesions should not be presumed to represent relapse: anchoring, availability, and confirmation biases need to be actively countered through deliberate type 2 thinking, broad differential diagnosis, and clinicopathological correlation.

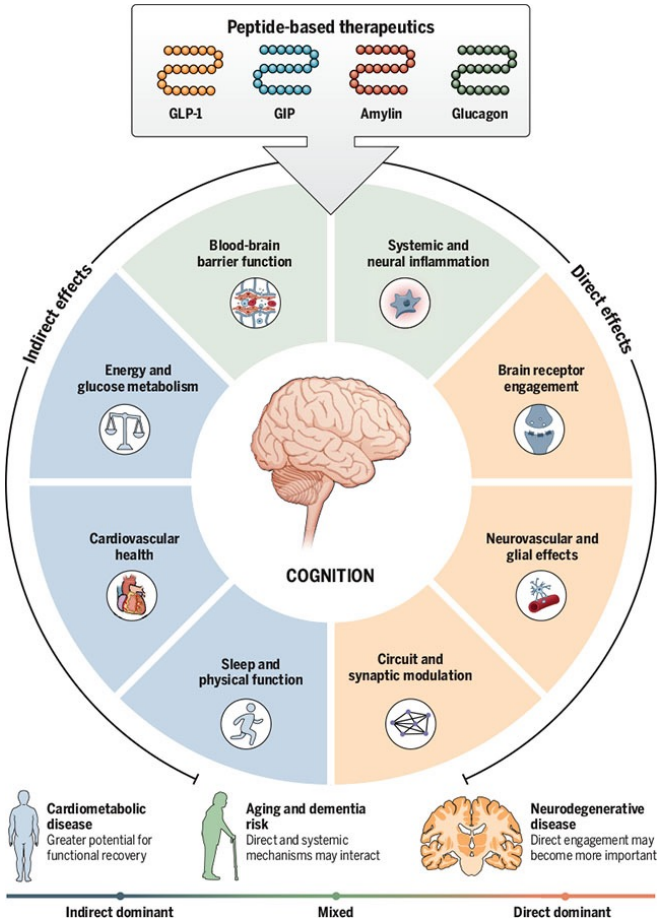



# Obesity pharmacotherapies and cognition

Pharmacotherapies for obesity and type 2 diabetes are increasingly being evaluated for their effects on cognition and brain health. Evidence from preclinical models, observational cohorts, and clinical trials has intensified interest, but findings remain mixed. A central challenge is to determine whether potential cognitive effects arise from direct actions on neural circuits, indirect consequences of improved cardiometabolic health, or both. This review examines the evidence across cardiometabolic disease, aging, and Alzheimer's disease, focusing on glucagon-like peptide-1 (GLP-1)–based therapies and combination approaches that engage glucose-dependent insulinotropic polypeptide, glucagon, and amylin pathways. We assess how receptor pharmacology, brain exposure, metabolic context, and disease stage shape cognitive outcomes and discuss how mechanistic clarity could guide therapies aimed at preserving or improving cognition.

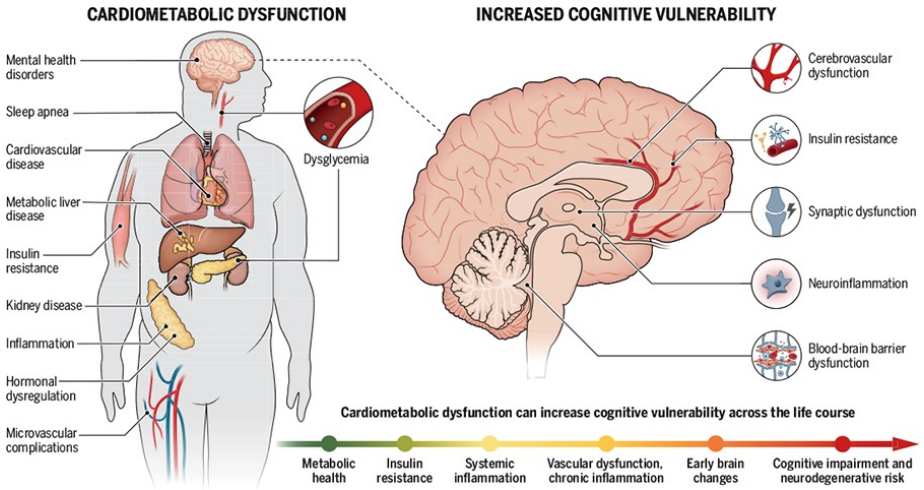



**Brain distribution of receptors targeted by obesity pharmacotherapies.** Sagittal schematic of a rodent brain showing reported expression of GLP-1, GIP, amylin, and glucagon receptors across brain regions implicated in learning, memory, executive function, motivation, and reward. Selected projections from brainstem GLP-1 neurons and mesocortical, mesolimbic, and nigrostriatal pathways are indicated. The median eminence and area postrema are highlighted as circumventricular regions with incomplete blood-brain barrier protection and potential access for circulating therapeutics. Receptor expression does not necessarily establish pharmacologically relevant drug exposure or functional engagement. AMY, amygdala; AMYR, amylin receptor; BNST, bed nucleus of the stria terminalis; CALCR, calcitonin receptor; CB, cerebellum; DVC, dorsovagal complex; EC, entorhinal cortex; GCGR, glucagon receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1R, glucagon-like peptide-1 receptor; HT, hypothalamus; LS, lateral septum; NAc, nucleus accumbens; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; PPG, preproglucagon; SN, substantia nigra; TH, thalamus; VTA, ventral tegmental area.




**Direct, indirect, and interacting pathways through which obesity pharmacotherapies may influence cognition.** Obesity pharmacotherapies targeting GLP-1, GIP, amylin, and glucagon pathways may affect cognition through systemic improvements in cardiometabolic health, sleep, and physical function; through direct engagement of neural, glial, and neurovascular targets; or through mechanisms shared across both routes. Their relative contribution is likely to vary with metabolic context and disease stage but remains incompletely defined.

GLP-1 receptor agonists (such as liraglutide, semaglutide, and dulaglutide) do not act as general cognitive enhancers for healthy individuals, and clinical trials have **not** shown them to reverse or improve established Alzheimer's disease or advanced dementia.




**Cardiometabolic disease and cognition.** Conceptual overview of how obesity, T2D, insulin resistance, vascular dysfunction, and inflammation may contribute to cognitive impairment across aging and neurodegenerative disease. Additional factors including hypoglycemia, renal and microvascular disease, sleep apnea, depression, and frailty may modify cognitive risk.

**Conclusions and future directions**

Current obesity pharmacotherapies clearly alter biological processes relevant to cognition, but reliable cognitive benefit has not been established across clinical settings. The most consistent evidence suggests a lower risk of cognitive decline or dementia in people with cardiometabolic disease, although these findings remain largely observational, whereas effects on specific cognitive abilities are inconsistent. Trials in established AD have not demonstrated clinical efficacy, and enhancement in metabolically healthy individuals remains largely speculative. The central question is therefore not simply whether obesity pharmacotherapies affect cognition but which patients may benefit, at what stage of disease, and under which treatment conditions.

# This type of exercise is surprisingly good at lowering blood pressure



If it feels like current events are conspiring to raise your blood pressure, now might be a good time to go sit against a wall for a few minutes.

In a new study, several minutes of wall sits — also called wall squats — three times a week effectively lowered people's blood pressures over time. Those gains lingered even if people cut back to doing only a few wall sits once or twice a week.

The findings add to existing evidence that wall sitting may "reduce blood pressure more than other forms of exercise," said Jonathan Wiles, a professor of exercise science at Canterbury Christ Church University in England, who oversaw the new study.

The time commitment may be much smaller than you'd expect, and starting with a very shallow sit — just bending your legs a bit — can be an effective way to begin.

Even people "who struggle to find the time and motivations to exercise" might be able to gain and hold on to the pressure-lowering benefits of wall squats, Wiles said.

## Why wall squats are good for your blood pressure

To do a wall squat, find an unadorned wall, lean against it and walk your feet out as you slide down the wall until your thighs are as close to parallel with the ground as feels comfortable.

Few of the study participants sat deeply, at first. For most, their knees were “not at 90-degree angles,” Wiles said. They sat, instead, at whatever depth they could maintain.

The goal was to hold that pose for two minutes at a stretch.

Wall squats involve isometric contractions, meaning that during the exercise, your muscles, held in one position, tighten and generate force, but don’t lengthen or shorten. (Muscles shorten during concentric contractions, such as raising a dumbbell, and lengthen during eccentric ones, like lowering that dumbbell again.)

A wealth of past studies show that isometric exercises lower blood pressure, both immediately and in the long term. Isometric contractions squeeze blood vessels inside muscles, temporarily reducing blood flow. Then, when the contraction stops, the blood gushes back, sparking the release of biochemicals that widen vessels and help them stay flexible and responsive, keeping blood pressure under control.

In a 2023 review of 270 exercise studies, researchers, including Wiles, concluded that isometric workouts lowered blood pressure more effectively than any other exercise, except possibly running.

Dive deeper

## Lower blood pressure in 4 weeks

In the years that Wiles and his colleagues have been studying isometric exercise, they’ve developed and tested a simple routine that reliably lowered people’s blood pressure in experiments within about a month.

You sit against the wall for two minutes, stand, sit on an actual chair or otherwise rest for two minutes, and repeat that sequence three more times, for a total of four bouts of wall sitting during eight minutes of total exercise.

BMJ Open Sport & Exercise Medicine



Various approaches to isometric exercise training

# Isometric exercise training and blood pressure control: exploring the dose-response to training frequency in a randomised controlled trial


## Abstract

**Background** Isometric exercise training (IET) is a time-efficient intervention that consistently demonstrates clinically meaningful reductions in resting blood pressure (BP). The optimal frequency required to maintain these benefits has not been established. This study aimed to (1) examine the dose–response relationship between training frequency and the maintenance of BP reductions following an initial 4-week IET period and (2) investigate the physiological mechanisms underpinning any observed changes in BP.

**Methods** Adults (n=100) with normal to high-normal BP were randomised into five groups: 3×, 2×, 1× or 0× IET sessions/week following an initial 4-week lower-body IET protocol (3×/week), or control. Haemodynamic and cardiac autonomic variables, including resting BP, total peripheral resistance (TPR), heart rate variability (HRV) and baroreceptor reflex sensitivity (BRS) were assessed at baseline, following the initial intervention (week 4), and following the maintenance period (week 8).

**Results** All intervention groups showed significant reductions in systolic BP (sBP), diastolic BP and mean arterial pressure (MAP) after 4 weeks compared with control (−9.45±6.69 mm Hg, $p<0.001$, −5.47±9.92 mm Hg, $p=0.007$ and −6.80±7.77 mm Hg, $p<0.001$, respectively). At week 8, the 1×, 2× and 3×/week groups maintained sBP and MAP reductions, although the magnitude of these reductions was significantly greater in the 3×/week group ($p<0.001$). The 0×/week group showed reversal of BP reductions to levels not significantly different from control. Only the 3×/week group maintained improvements in TPR, HRV and BRS.

**Conclusions** A reduction in IET frequency to 1–2 sessions per week can partially attenuate the rate at which BP adaptations regress during short-term reductions in training frequency.